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AMYOTROPHIC LATERAL SCLEROSIS AND RELATED CONDITIONS

A CLINICAL ANALYSIS

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The use of vitamin E in the treatment of amyotrophic lateral sclerosis has resulted in a controversy among neurologists. One group of investigators [1] feels that vitamin E cures or arrests the progress of the disease, whereas others [2] are equally certain that this substance is ineffectual.

In looking for an explanation of this wide difference in opinion the following questions arise: (*a*) What are the essential features of amyotrophic lateral sclerosis? (*b*) Are all investigators of this problem using the same criteria for its diagnosis? (*c*) What is the natural course of the disease when untreated—do all cases progress to death,

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1. Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**:10-13, 1940. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, J. A. M. A. **114**:948-959 (March 16) 1940; The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**:765-778, 1940. Alpers, B. J.; Gaskell, H. H., and Cantarow, A.: Effect of Vitamin E on the Muscular Dystrophies, Arch. Neurol. & Psychiat. **45**:364-366 (Feb.) 1941.

2. Shelden, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha-Tocopherol) Therapy in Certain Neurologic Disorders, Proc. Staff Meet., Mayo Clin. **15**:577-580, 1940. Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of the Neuromuscular Apparatus, Arch. Neurol. & Psychiat. **45**:672-679 (April) 1941. Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), J. A. M. A. **116**:1893-1895 (April 26) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B_6: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, ibid. **116**:1895-1896 (April 26) 1941.

or is it possible that some patients get well or the disease fails to progress after the initial involvement?

In an attempt to answer these and other questions, the following clinical analysis was undertaken. In order to overlook no cases of recovery, as well as to compare amyotrophic lateral sclerosis with other clinically related conditions, cases of progressive muscular atrophy, bulbar palsy and lateral sclerosis were also included in the study.

The following report is based on a study of the records of 151 cases in which the condition was classified as amyotrophic lateral sclerosis, 23 cases in which it was classified as progressive muscular atrophy (all types), 4 cases in which it was classified as progressive bulbar palsy and 19 cases in which it was classified as primary lateral sclerosis. These represent all satisfactory records of these conditions which were observed in the Neurological Institute of New York during the past ten years. A slight reclassification of the cases was made in certain categories as the study progressed, and is embodied in the discussion and the table.

In order to emphasize both their similarities and their differences, each group of cases was first analyzed separately; then, without regard for their hospital diagnoses, all were tabulated together and reclassified on the basis of their chief clinical manifestations, namely, evidence of lateral sclerosis, amyotrophy and muscular fibrillations. The presentation of the following materials is based on this final classification.

AMYOTROPHIC LATERAL SCLEROSIS

I. CLASSIFICATION

The cases of this disease have been classified under three clinical types: the complete, or Charcot; the atypical, and the incomplete. They will be discussed in that order.

A. Complete, or Charcot, Type.—There were 96 readily identified examples of amyotrophic lateral sclerosis which were designated here as being of the complete type. The patients presented well developed evidences of lateral sclerosis, amyotrophy and muscular fibrillations at the time they entered the hospital. There was wasting of the muscles of both upper extremities, most pronounced in the hands, but occurring to a variable extent also in the forearms, the arms and the shoulder girdles. Mild amyotrophy was frequently present also in the lower extremities, and in some instances this was marked. It was not so obvious, however, that the distal parts of the lower extremities suffered more than the proximal. The neck musculature frequently became involved soon after that of the shoulder girdle, but the muscles of the back, chest and abdomen usually suffered later. Fascicular muscular

twitchings [3] appeared early, before amyotrophy was evident, and were usually to be seen, off and on, until atrophy had become marked. They were easily identified in the musculature of the shoulder girdles, arms and thighs and could usually be demonstrated in other atrophying muscles as well. Developing bulbar amyotrophy was present in 45 of the 96 cases of the complete type. In 34 instances it followed, and in 11 instances it preceded, the development of amyotrophy elsewhere. Pyramidal tract disease was present in all of the 96 cases of the complete type, although its intensity varied greatly. Many patients exhibited a spastic gait, whereas hyporeflexia, due to advanced amyotrophy, was observed in others. These features will be discussed in greater detail later. No distinction between cases was made on the basis of whether the lesions in the pyramidal tract preceded or followed the amyotrophy, except as will be apparent later in connection with lateral sclerosis with fascicular twitchings.

The examples of complete amyotrophic lateral sclerosis just described conformed roughly with Charcot's original description of the disease.[4] Many of them would not be considered typical by Charcot, since his description was somewhat rigid. In recent years, however, there has been a tendency to broaden these limits. This is reflected in recent textbooks of neurology.[5] It should also be noted that relatively few cases of far advanced disease were studied; such cases are to be found more frequently in hospitals for chronic disease.

B. Atypical Type.—Cases of the atypical type presented the essential features of the disease, namely, lateral sclerosis, amyotrophy and muscular fibrillations. However, the distribution of the amyotrophy in all cases, and of the lateral sclerosis in 1 case, was distinctly unusual when the patient entered the hospital. In 5 instances the amyotrophy and fascicular twitchings were present in one extremity (monoplegic type)—in 2 cases in an upper, and in 3 others in a lower, extremity. In 2 of these cases there was beginning, or questionable, slight weakness in one other extremity, but in the other cases no additional amyotrophy, including the bulbar form, could be demonstrated. In these

3. This term is used interchangeably with muscular fibrillations and muscular fasciculations. It is felt that fascicular muscular twitchings, or simply fascicular twitchings, is a more specific term than either of the others. It is intended that it convey the same meaning as Denny-Brown and Pennybacker (Brain **61**:311-334. 1938) have given to the term "muscular fasciculations."

4. Charcot, J. M.: Lectures on the Diseases of the Nervous System: Second Series, London, New Sydenham Society, 1881.

5. (*a*) Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vols. 1-2. (*b*) Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940. (*c*) Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1934. (*d*) Bing, R.: Textbook of Nervous Diseases, translated by W. Haymaker, St. Louis, C. V. Mosby Company, 1939.

cases there was slight to moderate pyramidal tract disease. Only 1 case of hemiplegic type was noted. In this case the right leg and arm of the patient were weak and wasted, whereas the left extremities appeared normal. There were also early bulbar paralysis, with beginning atrophy of the tongue, and changes referable to the pyramidal tract, most noticeable on the amyotrophic side. In 10 additional cases the amyotrophy and muscular fibrillations were severe in the lower extremities and lacking or slight in the upper extremities (lumbar type). In 2 of these cases mild bulbar paralysis was exhibited. In each of the 10 cases the pyramidal tracts were involved to a variable degree.

Cases of the atypical type just considered have been described by many investigators. A bibliography and a discussion of them are available in Wilson's [5a] textbook of neurology. Our follow-up studies and the experiences of others, cited by Wilson,[5a] indicate that most of these cases eventually develop into more or less typical examples of the complete, or Charcot, type. It also appears that the so-called lumbar type, in which amyotrophy develops in the lower extremities first, occurs more commonly than is ordinarily believed. In many of these cases the hyperactive reflexes and the positive Babinski sign probably disappear when amyotrophy becomes extreme. The clinical picture then constitutes the pseudopolyneuritic type.[6] Cases of this type will be considered in detail in the section on progressive muscular atrophy with fascicular twitchings.

Proximal Type: Another group of 5 cases of the atypical form belongs with those in which both the upper and the lower motor neurons are involved, but in them the onset and sequence of amyotrophy were distinctive. In these cases amyotrophy with fasciculations developed in the proximal muscles of the extremities, i. e., in the shoulder girdles in all cases and less frequently in the arms, neck, thighs, hips and back. Later, in a few instances, the forearms and hands became involved. In 2 instances mild bulbar paralysis was exhibited. Pyramidal signs were definite in 4 cases and questionable in 1. Cases of this type have been reported before,[7] and the disorder is described in textbooks of neurology as the scapulohumeral type.[5c] According to Dana,[7] Grinker [5c] and observations in the present investigation, the course

6. (*a*) Patrikios, J. S.: Contribution à l'étude des formes cliniques et de l'anatomie pathologique de la sclérose latérale amyotrophique, Thesis, Paris, no. 149, 1918. (*b*) Foix, M.; Chavany, and Bascourret: Etude anatomo-clinique d'un cas de sclérose latérale amyotrophique à forme pseudo-polynévritique, Rev. neurol. **32**:822-826, 1925. (*c*) Wohlfart, S.: Die vordere Zentralwindung bei Pyramidenbahnläsionen verschiedener Art; eine histopathologische Untersuchung, Acta med. Scandinav., 1932, supp. 46, pp. 1-235. (*d*) Friedman, E. D.: Atypical Amyotrophic Lateral Sclerosis, New York M. J. **118**:422-425, 1923.

7. Dana, C. L.: Progressive Muscular Atrophy: A Study of the Causes and Classifications, with the Report of an Autopsy, J. Nerv. & Ment. Dis. **33**:81-100, 1906.

of this variant of the disease is relatively mild. In 2 of the cases in this series follow-up data were available. In 1 instance the total duration of the disease was sixteen months and in the other ninety-eight months. Another case, not in this series, was recently observed. The patient had been ill for six years and exhibited pronounced atrophy and weakness of the proximal muscles, fascicular twitchings and unilateral pyramidal tract disease, but was able to carry on with his office work six days a week.

Bulbar Type: In 5 additional cases the amyotrophy was limited to (3 cases) or chiefly concerned (2 cases) muscles innervated by cranial nerves. In each of these cases there was mild or moderate involvement of the pyramidal tracts. Follow-up studies revealed that in at least 2 of these cases the more or less complete picture of amyotrophic lateral sclerosis developed before death. It should be pointed out that bulbar signs preceded general amyotrophy in 11 instances of the Charcot type of amyotrophic lateral sclerosis.

In 1 of this group of 5 cases of bulbar involvement the disease presented itself originally with ptosis and diplopia. Later these symptoms cleared up; dysarthria and dysphagia developed, and, finally, amyotrophy appeared in the lower extremities and hyperactive reflexes in all extremities. Von Graefe [8] first suggested that progressive ophthalmoplegia could be related to the bulbar paralysis of amyotrophic lateral sclerosis. Other investigators have more recently pointed out this relationship, but absence of satisfactory pathologic studies precludes any definite settlement of the problem.[5a]

C. Incomplete Type.—This type includes three dissimilar subtypes, in which the clinical picture was dominated by evidences of lateral sclerosis, amyotrophy and bulbar palsy respectively.

1. Lateral Sclerosis with Fascicular Twitchings: There were 9 cases in this group. The course was rapidly progressive, and the patient exhibited hyperactive reflexes, especially in the lower extremities, frequently bilateral Babinski signs and occasionally absence of abdominal reflexes. In most of the cases a spastic gait occurred; in 6, urgency of urination, and in all but 1, in which the course was of short duration after admission to the hospital (six months), muscular fibrillations were exhibited. In the last case the course of the disease was rapidly progressive and accompanied by urgency of urination, both of these characteristics suggesting that the case belonged to this group. In 1 case there was questionable bulbar amyotrophy. Subsequent studies revealed that in at least 5 of the 9 cases in this group (all that could be followed) amyotrophy developed before death, and the pres-

8. von Graefe, in Eulenburg, A.: Lehrbuch der Nervenkrankheiten, Berlin, A. Hirschwald, 1878, vol. 2; cited by Wilson.[5a]

ence of fibrillations strongly suggested a similar destiny in 3 others. The inclusion of these cases as instances of a type of amyotrophic lateral sclerosis seems quite justified in view of the ultimate development of amyotrophy in more than half of them. It is of interest in this connection that in 6 of 8 cases of lateral sclerosis studied by Spiller [9] degenerating ventral horn cells were found at autopsy.

2. Progressive Muscular Atrophy with Fascicular Twitchings: There were 26 cases in this group (19 of them had been diagnosed as instances of amyotrophic lateral sclerosis and 7 as progressive neuropathic muscular atrophy, Aran-Duchenne type). Amyotrophy appeared first in the distal parts of the upper extremities in 12 cases, in the proximal parts of the upper extremities in 4 others, in the lower extremities in 8 cases and in all extremities simultaneously in 2 others. In 5 cases some bulbar involvement, usually slight, was exhibited, and in 2 of these the disease was ushered in by bulbar paralysis. In all cases muscular fibrillations appeared early and were followed and accompanied by muscular atrophy. No definite signs of pyramidal tract disease were found in any of the cases of this group, although in 3 instances they may have been obscured by severe amyotrophy in the lower extremities.

The problem of classifying cases of progressive muscular atrophy is difficult, since the evidences of pyramidal tract involvement, i. e., spasticity and extensor plantar responses, may have been masked by the presence of severe amyotrophy.[10] Furthermore, barely detectable or slight degeneration of the pyramidal tracts may not produce abnormal reflexes. This is indicated by the presence of normal deep reflexes and flexor plantar responses in cases of progressive muscular atrophy in which some degeneration of the pyramidal tracts has been observed post mortem.[11] This aspect of the problem has been reviewed recently by Wilson.[5a] On the other hand, there seem to be a few "pure" exam-

9. Spiller, W. G.: Primary Degeneration of the Pyramidal Tracts: A Study of Eight Cases with Necropsy, Univ. Pennsylvania M. Bull. **17**:390-407, 1904.

10. (*a*) Ottonello, P.: Sulla sclerosi laterale amiotrofica (Contributo clinico ed anatomo-patologico), Rassegna di studi psichiat. **18**:221, 397 and 557, 1929. (*b*) Marburg, O.: Amyotrophische lateral Sklerose, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936. (*c*) Wohlfart, G., and Swank, R. L.: Pathology of Amyotrophic Lateral Sclerosis: Fiber Analysis of the Ventral Roots and Pyramidal Tracts of the Spinal Cord, Arch. Neurol. & Psychiat. **46**:783-800 (Nov.) 1941.

11. Boukis, C.: Zur Frage der spinalen Muskelatrophien, Monatschr. f. Psychiat. u. Neurol. **96**:1-12, 1937. Hassin, G. B.: Amyotrophic Lateral Sclerosis: Anatomic and Pathologic Considerations, Arch Neurol. & Psychiat. **43**:765-777 (April) 1940; correction, ibid. **43**:1056 (May) 1940. Wohlfart and Swank.[10c]

ples of progressive muscular atrophy in the literature, although none of these have been studied by means of newer methods.[12]

One might be tempted to conclude that there are two distinct groups of cases in which the condition is diagnosed as progressive muscular atrophy, those with lesions of the pyramidal tracts which produce no signs, or in which the signs are masked by amyotrophy, and those in which the older methods of investigation have revealed no degeneration of the pyramidal tracts. The application of newer methods, such as fiber analysis,[13] to the study of the spinal cords in cases of the latter type may show that in many, if not all, of them degenerated pyramidal tract fibers are present, although sclerosis may not yet be evident. It has been shown in cases of amyotrophic lateral sclerosis that approximately 50 per cent of the large nerve fibers in the ventral spinal roots may be absent before ordinary microscopic examination reveals the defect. This appears to be true of the pyramidal tract areas as well. Moreover, sclerosis may not be observed there, even though a reduction in the number of large nerve fibers can be detected in fiber analysis preparations.[10c] It must be remembered that the production of glial tissues and of the picture of sclerosis takes time. In the final analysis there will probably be a small number of cases of progressive muscular atrophy with normal pyramidal tracts, and in these instances one may assume that there was insufficient time for degeneration to occur. Under the circumstances it seems expedient to consider progressive muscular atrophy as an incompletely developed phase of amyotrophic lateral sclerosis. The investigators who have expressed themselves both for and against this concept are too numerous to be listed here; the older literature on this subject has been reviewed by Rhein.[12b]

The problem of classifying primary lateral sclerosis is somewhat similar, since in pure clinical examples of pyramidal tract disease changes in the ventral horn cells characteristic of amyotrophic lateral sclerosis have been shown.[9] Here, again, studies with the aid of modern methods are lacking.

3. Progressive Bulbar Palsy: There were 3 cases in this group, none with pyramidal disease. In 2 of these cases there was amyotrophy of a slight degree, aside from that in relation to the cranial nerves. In these cases the illness frequently terminates as the result of aspiration pneumonia, so that the complete picture of amyotrophic lateral sclerosis may not have time to develop. As noted before, in 11 cases of com-

12. (*a*) Alzheimer, A.: Ueber einen Fall von spinaler progressiver Muskelatrophie mit hinzutretender Erkrankung bulbärer Kerne und der Rinde, Arch. f. Psychiat. **23**:459-484, 1892. (*b*) Rhein, J. H. W.: Amyotrophic Lateral Sclerosis: A Pathological Study of an Early Case, New York M. J. **105**:915-919, 1917.

13. Häggqvist, G.: Analyse der Faserverteilung in einem Rückenmarksquerschnitt, Ztschr. f. mikr.-anat. Forsch. **39**:1-34, 1936. Wohlfart and Swank.[10e]

pletely developed amyotrophic lateral sclerosis the first manifestation of the disease was bulbar paralysis. The early development of bulbar signs has been noted by other investigators.[14] The theoretic problems are similar to those already considered in connection with progressive muscular atrophy with fibrillations.[15]

II. CHARACTERISTIC FEATURES OF AMYOTROPHIC LATERAL SCLEROSIS

A. Fibrillary Muscular Twitchings.—Fibrillations were an almost constant feature of amyotrophic lateral sclerosis, being absent only in the most atrophic muscles. In a few instances, however, they were found only after a diligent search. They appeared early, before weakness or atrophy was evident, and were present until the amyotrophy had become severe. They were observed most frequently in the shoulders, arms and thighs, much less frequently in the hands.

These twitchings appeared to be of great importance in determining the rapidity of the course of the disease, few fibrillations indicating a slow, and many and widespread fibrillations a rapid, course. In 23 cases of completely developed amyotrophic lateral sclerosis with marked and widespread fibrillations the total duration of the disease averaged twenty-seven months, with a maximum variation of from nine to fifty months. In 6 cases with occasional, yet definite, fibrillations the average total duration was fifty-eight months or more (in 3 cases the patients are still alive), with a maximum variation of twenty-four to ninety-six (or more) months. In spite of the fact that the muscular fibrillations observed in the hospital represent only a small "sample" and that fibrillations may vary from time to time, a fairly close correlation of these twitchings with the speed of progress of the disease could be demonstrated.

Pathologic and physiologic studies have shown that many muscle fibers are innervated by a single ventral horn neuron.[16] In amyotrophic lateral sclerosis these groups of muscle fibers degenerate together, producing a pathologic picture characteristic of this disease: groups of muscle fibers in various stages of atrophy surrounded by normal

14. Wechsler, I. S.: Bulbar Amyotrophic Lateral Sclerosis, Neurol. Bull. **3**:82-86, 1921.

15. Throckmorton, T. B.: Amyotrophic Lateral Sclerosis, J. Iowa M. Soc. **7**:177, 1917. Rhein.[12b] Wilson.[5a]

16. Porter, E. L.: Evidence That the Postural Tonus of Decerebrate Rigidity Increases in Amount by the Successive Innervation of Single Motor Neurons, Am. J. Physiol. **91**:345-361, 1929. Eccles, J. C., and Sherrington, C. S.: Numbers and Contraction-Values of Individual Motor-Units Examined in Some Muscles of the Limb, Proc. Roy. Soc., London, s.B **106**:326-357, 1930. Clark, D. A.: Muscle Counts of Motor Units: A Study in Innervation Ratios, Am. J. Physiol. **96**:296-304, 1931.

fibers.[17] It seems, from the work of Denny-Brown and Pennybacker,[18] that the muscular twitchings in this condition are repeated contractions of these motoneuron units.

Muscular twitchings closely resembling the fibrillations of amyotrophic lateral sclerosis may be seen inconstantly in a variety of conditions. They may be observed occasionally in cases of purulent meningitis, extramedullary tumor of the spinal cord and dementia paralytica [5d]; syringomyelia, inflammatory lesions of peripheral nerves and progressive hypertrophic polyneuritis [5b]; paralysis agitans, and infectious polyneuritis, compression of peripheral nerves and debilitating conditions, such as ulcerative colitis.[19] This would seem to indicate that more than one mechanism can produce muscular fibrillations. It has not been proved, however, that the muscular twitchings in each of these conditions are due to repeated contractions of motoneuron units, and it would seem impossible to determine this from clinical examination alone.

B. Signs of Pyramidal Tract Involvement.—In cases of amyotrophic lateral sclerosis signs of degeneration of the pyramidal tract seemed to appear in the following order: hyperreflexia, extensor plantar responses and, finally, absence of cremasteric and abdominal reflexes. The first manifestation was always hyperreflexia in the lower extremities and, later, in the upper. The hyperreflexia usually became pronounced before the next sign of pyramidal tract disease, the positive Babinski sign, appeared. The latter was present in 43 of 112 instances of the completely developed and atypical forms of amyotrophic lateral sclerosis and in 6 of 9 cases of lateral sclerosis with fibrillations. In 31 of the 49 cases with a positive Babinski sign the abdominal reflexes were present, and in the remaining 18 cases they were absent. In another 26 cases the abdominal reflexes were absent and the Babinski sign was negative. The last group of cases was especially difficult to evaluate, as the abdominal reflexes are so frequently disturbed in elderly, and especially in emaciated, persons. Furthermore, degeneration of the peripheral nerves could not be ruled out.

17. Durante, G., in Cornil, V., and Ranvier, L.: Manuel d'histologe pathologique, ed. 3, Paris, Felix Alcan, 1902, vol. 2, pp. 1-477. Wohlfart, G.: Untersuchungen über die Gruppierung von Muskelfasern verschiedener Grösse und Struktur innerhalb der primären Muskelfaserbündel in der Skeletmuskulatur, sowie Beobachtungen über die Innervation dieser Bündel, Ztschr. f. mikr.-anat. Forsch. **37**:621-642, 1935.

18. Denny-Brown, D., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311-334, 1938.

19. Personal observations and private communications from other observers.

The presence of flexor plantar responses in cases of amyotrophic lateral sclerosis with hyperactive reflexes has been noted before.[20] Also, in cases of lateral sclerosis due to Lathyrus sativus, Minchin [21] noted a high percentage of normal abdominal and cremasteric reflexes in patients with both hyperactive reflexes and a positive Babinski sign. This dissociation of the signs of upper motor neuron impairment may be useful in the differential diagnosis of lesions of the pyramidal tract.

Pseudobulbar palsy could be demonstrated in only 1 case. The patient exhibited advanced lateral sclerosis with hyperreflexia, spastic gait, a positive Babinski sign and absence of abdominal and cremasteric reflexes. Fascicular twitchings and emotional instability were also present. In other emotionally unstable patients with advanced pyramidal tract disease, however, pseudobulbar palsy may have been masked by the presence of bulbar amyotrophy.

Urgency of urination was a complaint in 25 cases of amyotrophic lateral sclerosis. In all but 4 of these cases the Babinski sign was positive, and in only 1 case was hyperreflexia the only evidence of impairment of the pyramidal tracts. A clear relationship of urgency to changes in the pyramidal tract was indicated by its presence in 6 of the 9 cases of lateral sclerosis with fibrillation and by its absence in patients with amyotrophy alone. Severe involvement of the pyramidal tracts was not always accompanied by urgency, however, since 4 patients with positive Babinski signs did not complain of this symptom.

Little attention seems to have been paid to urgency in cases of amyotrophic lateral sclerosis. Erb [22] noted it in 2 of his cases of lateral sclerosis, and Minchin, in 2 cases of lateral sclerosis due to lathyrism.[21] It is of interest that urgency occurred in only 1 of 21 cases of primary lateral sclerosis without fibrillations, in contrast to its presence in 6 instances of urgency among 9 cases of the more acute form of lateral sclerosis with fibrillation. Perhaps compensatory mechanisms have time to develop in cases of the more chronic form. Certainly, the presence of urgency in a patient with pyramidal tract disease only suggests that amyotrophic lateral sclerosis may develop. If fibrillations are also present the likelihood is increased.

Emotional instability was frequently associated with degeneration of the pyramidal tracts, although probably not due to it alone. This

20. Chatelin, C.: Le réflexe cutané plantaire en flexion dans la sclérose latérale amyotrophique, Rev. neurol. **21**:621-623, 1913. Monrad-Krohn, G. H.: Les réflexes plantaires dans la sclérose latérale amyotrophique, ibid. **32**:831-834, 1925. Brunschweiler: A propos du réflexe de Babinski dans la sclérose latérale amyotrophique, ibid. **32**:848-851, 1925.

21. Minchin, R. L. H.: Primary Lateral Sclerosis of South India (Lathyrism Without Lathyrus), Brit. M. J. **1**:253-255, 1940.

22. Erb, W.: Ueber die spastische Spinalparalyse (tabès dorsal spasmodique. Charcot), Virchows Arch. f. path. Anat. **70**:241-267, 1877.

symptom was prominent in 9 cases of pronounced bulbar amyotrophy. In these cases the evidences of pyramidal tract involvement ranged from hyperreflexia to this sign plus extensor plantar responses and absence of abdominal reflexes. In many other cases, however, of just as severe bulbar amyotrophy, and also of marked impairment of the pyramidal tracts, this symptom was not present. One is forced to conclude that although degeneration of the bulbar nuclei, as well as impairment of the pyramidal tracts, is frequently associated with emotional instability in cases of amyotrophic lateral sclerosis, the underlying cause of the emotional instability is probably neither of these pathologic changes.

Davison and Kelman [23] have recently reported a large group of cases of pathologic laughing and crying. Two of their cases were instances of amyotrophic lateral sclerosis, and in a third the disturbance corresponded to what has been referred to here as lateral sclerosis with fascicular twitchings. They concluded that no one region of the brain controls or produces this emotional instability, but that many cortical areas, including the frontal, premotor, motor, parietal, temporal and hippocampal, may be responsible, since they are centers for integration of affective responses. The hypothalamus or other diencephalic nuclei appear to be the main centers for release of these responses, however.

C. Bulbar Amyotrophy.—This feature was noted in 45 cases of the complete, 5 cases of the atypical and 8 cases of the incomplete type of amyotrophic lateral sclerosis (progressive muscular atrophy and fibrillations). Its incidence was roughly the same in each of these conditions, whereas with lateral sclerosis with fibrillations bulbar amyotrophy was infrequently associated (1 case). The muscles innervated by the twelfth cranial nerve were involved in all cases with bulbar amyotrophy. The next most frequently affected muscles were those innervated by the ninth and tenth nerves, then those innervated by the lower part of the seventh nerve and, finally, those supplied by the masticator division of the fifth nerve. In almost all cases involvement of the cranial nerves appeared to be ascending in character, affecting first the hypoglossal nerve, then the glossopharyngeal and vagus nerves and the lower part of the facial nerve and, finally, the masticator division of the fifth nerve. The spinal accessory nerve was not considered with the remaining cranial nerves, since its motor division arises from the cervical portion of the spinal cord and atrophy of the sternocleidomastoid and trapezius muscles was frequently independent of changes in the other cranial nerves.

D. Pain.—Pains, of a varying character, were complained of by more than half the patients, but objective sensory changes were always

23. Davison, C., and Kelman, H.: Pathologic Laughing and Crying, Arch. Neurol. & Psychiat. **42**:595-643 (Oct.) 1939.

lacking. Of an unselected group of 45 cases of completely developed amyotrophic lateral sclerosis, cramps and a tightness in the legs were complained of in 12. These seemed to be related to involvement of the pyramidal tracts. A tired or fatigued feeling or a dull ache was complained of in 11 cases, and numbness, coldness or burning, in 6 others. These pains were frequently complained of early, before the true nature of the condition was recognizable, and then were the main source of annoyance. Pain in the lower part of the back and the neck were common in cases of advanced amyotrophy, probably because the joints had lost their muscular support.

Clinical Data in One Hundred and Ninety-

	No. of Cases	Age of Onset (Years)							Sex Incidence		Urgency of Urination	Emotional Instability	On Admission to Hospital						
		10	20	30	40	50	60	70—	M	F			½	1	2	4	6	8	10
Primary lateral sclerosis.....	21	2	1	..	6	6	5	1	8	13	1	1	..	3	..	7	2	2	4
Amyotrophic lateral sclerosis																			
Lateral sclerosis with fascicular twitchings.....	9	..	..	..	2	3	3	1	3	6	6	1	4	3	1	1	..	..	..
Complete type (Charcot)...	96	..	..	3	21	29	31	12	73	23	18	8	22	34	24	11	..	..	..
Atypical form *.....	16	..	..	1	1	6	7	1	12	4	2	0	2	8	3	3	..	..	..
Proximal type.....	5	..	..	..	1	1	2	1	5	0	1	0	2	1	2	..	..	..	..
Bulbar type (with evidences of pyramidal tract degeneration).....	5	..	..	..	..	2	2	1	2	3	0	2	2	3	..	..	..	..	..
Progressive bulbar palsy...	3	..	..	..	..	..	3	..	1	2	0	0	..	..	2	1	..	..	..
Progressive muscular atrophy with fascicular twitchings.....	26	..	..	2	4	7	9	4	22	4	0	0	7	8	7	4	..	..	..
Progressive muscular atrophy without fascicular twitchings.....	16	4	7	1	2	1	..	..	12	3	0	0	..	..	2	3	4	2	1

* Atypical forms include the monoplegic, hemiplegic and lumbar. The proximal type has been considered separately because the incidence of elevated protein was unusually high in cases of this form.

These subjective sensory complaints have been frequently remarked [24] and are considered of unusual occurrence.[5d] Their source is not at all clear, but possibly products of degeneration or of abnormal metabolism, which arise from the degenerating motor nerve fibers or muscle fibers, stimulate the neighboring sensory nerve fibers. Compression of sensory nerve fibers by contracting connective tissues which are replacing degenerated motor nerve fibers could also be a factor late in the disease, but probably not at its beginning.

E. Cerebrospinal Fluid Proteins.—The proteins of the cerebrospinal fluid were elevated above 40 mg. per hundred cubic centimeters in 55 cases of amyotrophic lateral sclerosis, and in 37 instances the protein

24. Wechsler, I. S.; Brock, S., and Weil, A.: Amyotrophic Lateral Sclerosis with Objective and Subjective (Neuritic) Sensory Disturbances: Clinical and Pathologic Report, Arch. Neurol. & Psychiat. **21**:299-310 (Feb.) 1929. Bing.[5d]

content was greater than 50 mg. per hundred cubic centimeters. The table shows the changes in the cerebrospinal fluid proteins which were observed in each type of the disease. It appears from the data that the proteins were affected more by lesions in the peripheral nerves than by those in the pyramidal tracts and that bulbar amyotrophy alone was associated with minimal changes in this substance. In 12 cases in which the proteins were above 70 mg. per hundred cubic centimeters there was severe general amyotrophy, whereas pyramidal signs were variable or absent (2 cases). In 6 of these cases there was severe, in 1 mild and in 5 no bulbar paralysis. The duration of the disease in

Cases of Amyotrophic Lateral Sclerosis and Related Conditions

Duration of Disease (Years)															Cerebrospinal Fluid Proteins (Mg./100 Cc.)					
At Death							In Patients Still Living								40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	90 and Above
1	2	4	6	8	10	15	4	6	8	10	15	20	25	30						
..	..	..	1	..	..	1	..	1	2	2	3	3	..	1	..	2	..	..	1	..
..	2	3	..	..	..	..	2	..	2	..	..	..	..	..	3	..	..	..	..	..
1	13	12	5	4	..	..	5	3	1	..	1	..	..	..	10	11	6	3	5	2
..	3	4	..	..	..	..	..	1	..	..	..	..	..	..	1	1	..	..	..	..
..	1	..	..	1	..	..	..	..	..	..	..	..	..	..	2	2	1	..	..	..
..	2	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..
..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..
1	3	3	2	1	..	..	3	1	..	..	..	..	..	..	1	1	3	1	1	..
..	..	..	..	1	..	1	1	3	1	3	2	3	..	..	..	1	..	1	1	..

these 12 cases varied from three to thirty months, in 7 cases being less than one year. In 6 of the 7 cases in which the illness was of one year's duration or less bulbar amyotrophy was severe.

In a group of cases of amyotrophic lateral sclerosis Merritt and Fremont-Smith [25] found the protein content of the cerebrospinal fluid elevated much as reported here. In all other respects, essentially, the cerebrospinal fluids were normal in both series of cases.

F. Vital Data.—These data, of which little unusual can be said, are presented in the table. The age of onset of amyotrophic lateral sclerosis was chiefly during the fourth, fifth and sixth decades of life. The sex incidence was approximately 3 males to 1 female, except in cases of lateral sclerosis with fibrillations and bulbar palsy, with or without involvement of the pyramidal tracts. In these cases there was a tendency

25. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1937.

for females to be more numerous than males. There was a somewhat higher incidence of amyotrophic lateral sclerosis among Jewish patients than would have been expected from the incidence of their admission to this hospital. This was especially noticeable in the complete, or Charcot, type. Otherwise, the racial incidence was not unusual, and almost all racial groups except the Chinese were represented. Reed [26] stated that the disease occurs with ordinary frequency in the Chinese.

Associated diseases were conspicuous by their infrequency. Diabetes mellitus occurred in 4 cases; secondary anemia, of unknown origin, in 2 cases; questionable pernicious anemia, in 1 case; hypertension, in 1 case; brain tumor, in 1 case; syphilis, in 1 case; osteoarthritis, in 1 case, and chronic myelitis, in 1 case. These conditions either had preceded or were present simultaneously with amyotrophic lateral sclerosis. Trauma was also conspicuous by its infrequency; in only 1 instance was there a clear time relation between the occurrence of appropriate injury and amyotrophy. Trauma frequently occurred after the onset of the disease, and then was due to the patient's motor impairment. Trauma as a causative factor has been investigated and discussed by others,[27] and it can be said that there is no clear or constant etiologic relationship between it and the onset of amyotrophic lateral sclerosis in this series.

Many years before the onset of what appeared to be amyotrophic lateral sclerosis, 3 patients, not included in this analysis, had had encephalitis, and 2 others, acute poliomyelitis. Salmon and Riley [28] have recently discussed the relationship of acute poliomyelitis to subsequent chronic amyotrophy. The present study has not materially clarified the relationship.

PRIMARY LATERAL SCLEROSIS WITHOUT FASCICULAR TWITCHINGS

Twenty-one cases have been included in this group. They were distinguished from the examples of acute lateral sclerosis with fibrillations by the very gradual, or insidious, onset of signs and symptoms of pyramidal tract disease. Hyperreflexia appeared first in the lower extremities in all cases. Later, in all but 7 signs of pyramidal involve-

26. Reed, A. C.: Nervous Diseases in China, Boston M. & S. J. **171**:638-643, 1914.

27. Waggoner, R. W., and Löwenberg, K.: The Role of Trauma in Amyotrophic Lateral Sclerosis, Tr. Am. Neurol. A. **65**:84-92, 1939. Turner, J. W. A.: Trauma and Progressive Muscular Atrophy, Lancet **2**:549-551, 1939.

28. Salmon, L. A., and Riley, H. A.: The Relation Between Chronic Anterior Poliomyelitis or Progressive Spinal Muscular Atrophy and Antecedent Attack of Acute Anterior Poliomyelitis, Bull. Neurol. Inst. New York **4**:35-63, 1935.

ment were present in the upper extremities, and in 1 pseudobulbar palsy with emotional instability developed. In all but 3 cases in this group extensor plantar responses were elicited, and in 11 of these abdominal reflexes were absent. Muscular fibrillations and amyotrophy were observed in none of these cases, and in only 1 was urgency of urination complained of. The course of the disease was slowly progressive, having a duration of more than five years in 11 cases and of more than ten years in 6 cases at the time the patient entered the hospital. In only 1 instance was the involvement of the pyramidal tract unilateral, as in the cases described by Mills.[29]

In many respects the evidences of impairment of the pyramidal tract in these patients were similar to those observed in amyotrophic lateral sclerosis. The signs were ascending in that they appeared in the lower extremities first and in the upper extremities later. In both conditions the order in which the neurologic signs developed was the same, i. e., hyperreflexia, extensor plantar reflexes and, finally, absence of abdominal reflexes. In cases of amyotrophic lateral sclerosis the chief distinguishing features were urgency of urination and the very rapid course. It is possible that urgency did not appear in cases of the more slowly developing lesions of the pyramidal tract because compensatory mechanisms had time to develop. The fact that the cerebrospinal fluid proteins were elevated to 88 mg. per hundred cubic centimeters in the 1 case in this group with urgency suggests that the course of the disease had recently become rapidly progressive and that perhaps amyotrophy would appear later. It is of considerable interest that the development of pyramidal signs in posterolateral sclerosis, as well as in amyotrophic lateral sclerosis, is similar.[30] An interesting discussion of the relationship of lateral sclerosis to amyotrophy on the one hand, and to posterior column disease, on the other, was given by Strümpell.[31]

A few facts relative to vital data are of interest. In cases of lateral sclerosis, with or without fibrillations, females were afflicted more frequently than males. Also, the incidence of both conditions in Jewish patients was lower than would be expected from the incidence of Jews admitted to this hospital. There was considerable variation in the age of onset in cases of lateral sclerosis without fibrillations, although in most cases the onset was in the fourth, fifth or sixth decade.

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29. Mills, C. K.: Unilateral Ascending Paralysis and Unilateral Descending Paralysis, J. A. M. A. **47**:1638-1645 (Nov. 17) 1906.

30. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy, Brain **52**:271-291, 1929.

31. Strümpell, A.: A Textbook of Medicine, translated from the thirteenth German edition by H. F. Vickery and P. C. Knapp, third American edition, New York, D. Appleton and Company, 1901.

In recent years there has been a tendency among neurologists to doubt the existence of pure examples of lateral sclerosis (aside from familial types). This tendency is to a limited extent supported by Spiller's [9] study of 8 cases, which clinically were examples of lateral sclerosis. In 6 of these, degenerating ventral horn cells were noted; in only 2 cases were the pathologic changes limited to the pyramidal tract areas. Erb,[22] Strümpell [31] and other early investigators expressed the belief, on the basis of pathologic studies, that pure cases of lateral sclerosis did exist, although in many instances clinically pure cases were shown later to be examples of posterolateral sclerosis or amyotrophic lateral sclerosis. Recent investigators seem to believe that modern methods of study would disclose even fewer examples of "pure" lateral sclerosis. Here, again, Wilson [5a] pointed out the gross absence of any such studies. Final judgment must be reserved, although it seems quite likely that a limited number of "pure" examples of lateral sclerosis do occur. For the purpose of prognosis it is of considerable value to recognize the clinical examples of this condition, since then life expectancy of the patients is much greater than is that of patients with lateral sclerosis plus muscular fibrillations.

PROGRESSIVE MUSCULAR ATROPHY WITH FEW OR NO FASCICULAR TWITCHINGS

There were 16 cases in this group. They were distinguished from cases of progressive muscular atrophy with fibrillations (incompletely developed amyotrophic lateral sclerosis) by an insidious onset and a slowly progressive course. The main feature in this group was amyotrophy. This appeared first in the distal parts of the extremities, and there became extreme. Usually muscular atrophy failed to progress central to the knee or lower portion of the thigh, in the lower extremities, and to the hand or forearm, in the upper extremities, so that spindle deformities resulted. In all cases the legs were involved, and in many the hands and forearms as well. Twice the lower and upper extremities became involved simultaneously. In 2 cases the trapezius, erector spinae and sternocleidomastoid muscles were also atrophic, so that the patient's head bobbed around like a ball balanced on the end of a seal's nose. In 3 instances deformities of the feet, i. e., equinovarus and pes cavus, were noted. These had appeared early and were well developed before much attention was paid to them.

The slowly progressive nature of this condition is illustrated in a case in which an interval of thirteen years occurred between involvement of the legs. Seven years later the hands became involved as well. Usually, however, both legs became affected within a year, and the hands as well within three to five years. After this initial involve-

ment of the extremities, further progress of the developing amyotrophy appeared to be arrested, and the patient's condition remained almost stationary, in many instances for years. All but 2 of the patients followed at this institute during the past ten years are still alive and little changed from the time they first entered the hospital. One of them died after an operation for gallstones. In the other patient the course of the disease had been slowly progressive for about six years. Fascicular twitchings were then noted in the shoulders for the first time, and in less than two years the patient died. This patient also exhibited hyperactive reflexes, a positive Babinski sign on one side and diminution in objective peripheral sensitivity of the extremities.

Fibrillations were notably absent in 12 and inconspicuous in 4 of these cases. Evidences of pyramidal tract disease were observed in 3 cases. These consisted of hyperreflexia in the lower extremities in 1 case, extensor plantar responses in another and hyperreflexia, extensor plantar responses and absence of the lower abdominal reflexes in the third. Urgency of urination was not noted in any case. It is worth while to point out that signs of involvement of the pyramidal tract developed in the same order in these cases as in cases of amyotrophic lateral sclerosis, only more slowly. In 3 instances, in all of which pyramidal signs were absent, the cerebrospinal fluid proteins were elevated to 51, 78 and 100 mg. per hundred cubic centimeters respectively. This increase appeared to be of no prognostic value.

Subjective sensory complaints were frequent, and objective sensory changes, usually with stocking and glove distribution, were observed in 4 cases. From the fact that the objective changes were demonstrated only after long-standing weakness and severe amyotrophy, it is possible that these sensory phenomena were secondary to degenerative and reparative changes which were taking place in the peripheral nerves. Presumably, the degenerated motor nerve fibers were gradually replaced by scar tissue. This tissue contracted and exerted pressure on the sensory nerve fibers, and sensory phenomena, both subjective and objective, resulted. This concept is not supported by the occurrence of peripheral sensory changes in cases of so-called scapuloperoneal amyotrophy,[32] since the amyotrophy in the upper extremities is proximal and separated from the area of sensory change by a variable distance.

The incidence of males in these cases was relatively high, 12 males to 4 females, and the racial incidence was not remarkable. The age of onset was early, before the twentieth year in 11 cases. The influence of heredity was apparent in 5 of the 16 cases, in 2 of which other members of the family were affected. In these cases the age of onset and

32. Davidenkov, S. N.: Scapuloperoneal Amyotrophy, Arch. Neurol. & Psychiat. **41**:694-701 (April) 1939.

the sex and racial incidences were not different from those for the group as a whole. However, the cases with a hereditary background were different from the remaining cases in the group in one particular, in that in 3 of them there were foot deformities, mentioned before. In 2 there were no such deformities.

In the 5 cases in this group with a hereditary background the disorder corresponded closely with the condition designated by the term peroneal, or the Charcot-Marie-Tooth type of progressive muscular atrophy.[33] In 3 of these cases foot deformities were noted, and in 2 objective as well as subjective sensory changes were present. In all other respects, with the possible exception of speed of progress, which cannot be checked now because all but 2 of the patients who could be followed are still alive, these cases were not to be definitely distinguished from the remaining 11 cases of nonhereditary disease. It should be noted that objective sensory changes were also demonstrated in 2 of the cases of the nonhereditary form.

A review of the literature relative to examples of the hereditary or familial form of progressive muscular atrophy (progressive muscular atrophy with few or no muscular fibrillations) revealed two noteworthy facts.[34] First, an extremely insidious onset of foot deformities is com-

33. Charcot, J. M., and Marie, P.: Sur une forme particulière d'atrophie musculaire progressive, souvent familiale, debutant par les pieds et les jambes et alteigmant les mains, Rev. de méd. **6**:97-138, 1886; cited by Symonds and Shaw.[34c] Tooth, H. H.: The Peroneal Type of Progressive Muscular Atrophy, Thesis, Cambridge, London, H. K. Lewis, 1866; cited by Symonds and Shaw.[34c]

34. (*a*) Siemerling, E.: Zur Lehre der spinalen neuritischen Muskelatrophie (Atrophia muscularis progressiva spinalis neuritica Bernhardt), (progressiven neurotischen oder neuralen Muskelatrophie Hoffmann), Arch. f. Psychiat. **31**:105-127, 1898. (*b*) Virchow, R.: Ein Fall von progressiver Muskelatrophie, Virchows Arch. f. path. Anat. **8**:537-540, 1855. (*c*) Symonds, C. P., and Shaw, M. E.: Familial Claw-Foot with Absent Tendon Jerks: A "Forme Fruste" of the Charcot-Marie-Tooth Disease, Brain **49**:387-403, 1926. (*d*) Eisenbud, A., and Grossman, M.: Peroneal Form of Progressive Muscular Atrophy, Arch. Neurol. & Psychiat. **18**:766-778 (Nov.) 1927. (*e*) Cavanaugh, W. J., and Tucker, H.: Progressive Neural Muscular Atrophy (Peroneal Type): Clinical Report of Two Cases in Brothers, Associated with Mental Symptoms, New Orleans M. & S. J. **81**:290-293, 1928. (*f*) Lhermitte, J., and Mouzon, J.: Amyotrophie du type Charcot-Marie à debut tardif. Prédominance familiale dans le sexe féminin, Rev. neurol. **67**:243-248, 1937. (*g*) Brownsberger, C. N., and Nielsen, J. M.: Progressive Spinal Muscular Atrophy with Sensory Changes: Possibility of Two Diseases, Bull. Los Angeles Neurol. Soc. **3**:182-185, 1938. (*h*) Schneider, D. E., and Abeles, M. M.: Charcot-Marie-Tooth Disease with Primary Optic Atrophy: Report of Two Cases Occurring in Brothers, J. Nerv. & Ment. Dis. **85**:541-547, 1937. (*i*) Ingham, S. D.: A Case of Transition Between Charcot-Marie-Tooth and General Form of Progressive Spinal Muscular Atrophy, Bull. Los Angeles Neurol. Soc. **3**:136-137, 1938. (*j*) Fitzgibbon, J. P.: Atypical Charcot-Marie-Tooth Disease Following Probable Poliomyelitis, ibid. **4**:136-138, 1939.

monly the initial manifestation of the disease. This was usually noted early in childhood or infancy. Notable exceptions to this rule are a case described by Lhermitte and Mouzon,[34f] with onset at the age of 52, and 1 case in this series, with onset at the age of 30. Second, cases of the familial type are apt to present features not ordinarily considered as a part of the general picture of progressive muscular atrophy —for example, optic atrophy,[34h] posterior column disease,[35] mental changes,[34e] nystagmus [34h] and scapular amyotrophy.[32] The sensory changes, said by Charcot, Marie and Tooth to be of infrequent occurrence, need no further emphasis. In a few cases evidences of pyramidal tract disease were also present.[36]

In commenting on the foot deformities, Symonds and Shaw [34c] stated that if the intrinsic muscles of the feet are affected first pes cavus develops, and if the peroneal and anterior tibial groups are involved first equinovarus results. These authors also pointed out that in the main postmortem examinations have been unsatisfactory and few, and have revealed a variable pathologic picture combined with degeneration of the anterior horn cells and of the ventral motor nerve roots. A study by Macklin and Bowman [37] of a family composed of 101 persons showed that approximately 50 per cent of the offspring of parents with the disease became afflicted.

The remaining 11 cases without hereditary or familial features appear to be cases of arrested amyotrophic lateral sclerosis, 8 of which were instances of the incompletely developed disease and might well be examples of slowly developing progressive muscular atrophy, and 3 of which might be examples of an arrested or slowly progressive form of the complete, or Charcot, type. In all of these cases muscular fibrillations were absent or inconspicuous. This is of interest in view of the fact that in cases of amyotrophic lateral sclerosis with few fibrillations the prognosis is better than in those with many fibrillations.

The relationship of the hereditary to the nonhereditary forms of progressive muscular atrophy with few or no fibrillations is uncertain. Clinically the cases may be similar, a transition from one form to the other being supplied by the 2 cases of nonhereditary type with sensory changes and the 2 cases of hereditary type without foot deformities. Although the fact is not clearly demonstrable here, a study of the literature and consideration of the cases included in this study indicate that the hereditary form of the disease was somewhat less rapidly progressive than the nonhereditary form. Also, the amyotrophy in cases of

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35. Siemerling.[34a] Virchow.[34b] Schneider and Abeles.[34h]

36. Brownsberger and Nielsen.[34g] Ingham.[34i]

37. Macklin, M. T., and Bowman, J. T.: Inheritance of Peroneal Atrophy, J. A. M. A. **86**:613-617 (Feb. 27) 1926.

the hereditary form tended to be limited to the more peripheral parts of the extremities. In both these respects an indistinguishable transition from one type to the other was present, and notable exceptions were encountered. In none of our cases of the hereditary form were evidences of pyramidal tract disease observed, but elsewhere,[36] as noted before, this has been reported.

COMMENT

Amyotrophic lateral sclerosis may be considered to be a steadily progressive, fatal disease of approximately one to six years' duration. Our data (table) do not indicate that its various clinical types, i. e., complete, incomplete and atypical, differ notably in their course, although it must be said that the prognosis increases in gravity as the clinical picture becomes more complete. This is to be expected, since the atypical form and in many cases the incomplete form become complete before death. The cerebrospinal fluid proteins were not always a reliable index of progression of the disease. It is true that elevation of proteins occurred in most of the cases of more rapidly progressive course, but in many cases of slowly progressive course this increase was also exhibited. The appearance of bulbar palsy must always be viewed with alarm, since this makes feeding difficult and may lead to the development of aspiration pneumonia.

The frequency and magnitude of muscular fasciculations appeared to be a reasonable indication of the speed of progress of the disease. As pointed out before, many fascicular twitchings indicated that the amyotrophy was developing rapidly, whereas few fibrillations were seen when it was more slowly progressive. It should not be forgotten, however, that only a small "sample" of fibrillations could be observed during the patients' stay in the hospital. Quite possibly, the fibrillations may have been entirely different either before or after this period. Despite this obvious source of error, a fairly close correlation could be demonstrated. This should be of value in prognosis, especially when patients can be observed from time to time over a longer period.

The prognosis in cases of either primary lateral sclerosis or progressive muscular atrophy without muscular fibrillations was surprisingly good. It is worth mentioning that the cerebrospinal fluid proteins were elevated in 3 cases of progressive muscular atrophy without fibrillations, the course of the disease in these cases being no different from that in the other cases in this group with normal cerebrospinal fluid proteins.

It was noted earlier in this paper that the 11 cases of nonhereditary progressive muscular atrophy without fibrillations might conceivably be instances of arrested or very slowly progressive amyotrophic lateral

sclerosis, 3 being of the complete, or Charcot, type and the remaining 8 of the incomplete type. Four additional cases classified as of the Charcot type, another as of the atypical (monoplegic) type and, finally, another as of the incomplete type (progressive muscular atrophy with fibrillations) can, it would seem, be added to these 11 cases. The progress of the disease in the last 6 cases was arrested, was very slowly progressive or, as in 1 case, was arrested and followed by improvement. All of the patients are still alive and have been ill for from five to eleven years.

More recently 3 similar cases have been observed at the Long Island Hospital, Boston. In 2 cases the condition was characterized by amyotrophy of about twenty-five years' duration. In 1 of these the muscular atrophy had developed rapidly over a period of two or three years and had since remained stationary. The patient had serologic evidence of syphilis.[38] In the second case the amyotrophy had been very slowly, but steadily, progressive, and bulbar amyotrophy had developed during the last six months. In the third case advanced amyotrophy, bulbar palsy and lateral sclerosis of eight years' duration were exhibited. Little progress had been noted in the patient's condition for several years, and recently she had gained in strength.

Thus, a total of 20 patients might be considered to have slowly progressive or arrested amyotrophic lateral sclerosis, 8 of them exhibiting signs of pyramidal tract disease plus amyotrophy, the remaining 12 manifesting only amyotrophy. Some of these patients noted that the disease had been rapidly progressive in the beginning, at which time others noted muscular twitchings. In the remaining patients the disease had been slowly and steadily progressive from the start. The problem at hand is to determine how frequently the course of the disease may be so prolonged. According to the present study, this may occur in at least 5 per cent, and in no more than 10 to 15 per cent of cases. Perhaps these have caused the controversy in connection with vitamin E therapy. Also, one must not overlook the influence of incidental conditions, such as cardiac failure and chronic sepsis, on neurologic conditions in general, and more specifically on amyotrophic lateral sclerosis. Their relief through specific and general therapies undoubtedly benefits the underlying condition.

If amyotrophic lateral sclerosis can become arrested, it seems reasonable to expect that very slowly progressive muscular atrophy can suddenly become rapidly progressive. This appears to have happened

38. It is quite likely that this patient's amyotrophy was due to syphilitic lesions in the spinal cord. This cause must be very uncommon, however, since only 1 case in the present series had serologic evidence of syphilis, and a past history of syphilis was almost as rare—a check revealing no past history of syphilis in 50 of the most recent cases.

in 1 case, in which for five or six years the amyotrophy had been very slowly progressive and without fascicular twitchings. Rather suddenly fibrillations developed in the shoulder girdles, and when the patient entered the hospital knee and ankle jerks were hyperactive and a Babinski sign was elicited on one occasion. In less than two years he died.

Problems of classification cannot be decided arbitrarily, especially since there are so few pathologic and no physiologic or biochemical data. Possibly all patients with amyotrophic lateral sclerosis die of the disease according to schedule, and the arrested or slowly progressive forms represent an entirely different condition. This concept is held by many investigators of the problem. Diagnosis, based on the latter concept, will many times be difficult because the forms of the disease are not demarcated into distinct groups but, rather, merge with one another. This spectral relationship was brought out in the large number of cases studied, and is represented schematically in the figure. Neither concept of the relationship of these conditions should lead to needless confusion in judging the efficiency of therapy if one recognizes that the course of the disease may be variable.

Examples of slowly progressive muscular atrophy have been described before, notably in the English literature by Dreschfeld [39] and Dana.[7] Both these authors reviewed the older literature and pointed out the apparent lack of familiarity of American and English writers with the condition. The relationship of syphilis in these cases is not at all clear. None of the cases in this series were complicated by this condition, whereas earlier writers expressed the belief that in most of their cases the disease was caused by syphilis. Amyotrophy due to syphilis is quite distinctive pathologically,[40] but conceivably could be confused with nonsyphilitic amyotrophy, especially if the blood and spinal fluid were not examined serologically.

The relationship of primary lateral sclerosis to amyotrophic lateral sclerosis is subject to the same dual interpretation; namely, the two conditions may be closely related, one being more slowly progressive than the other (figure), or they may be distinct and separate entities. It suffices to point out here that the clinical findings referable to the pyramidal tracts were the same in both instances, except that urgency of urination was infrequent in cases of slowly progressive primary lateral sclerosis and that in 6 of 8 clinical cases of primary lateral sclerosis pathologic studies showed degenerating ventral horn neurons.[9] It is

39. Dreschfeld, J.: On Some of the Rarer Forms of Muscular Atrophies, Brain **8**:164-190, 1885.

40. Martin, J. P.: Amyotrophic Meningo-Myelitis (Spinal Progressive Muscular Atrophy of Syphilitic Origin), Brain **48**:153-182, 1925. Putnam, T. J., and Alexander, L.: Tissue Damage Resulting from Disease of Cerebral Blood Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:544-567, 1938.

noteworthy that the signs referable to the pyramidal tract in cases of posterolateral sclerosis [30] may also be similar to those which were observed in cases both of amyotrophic lateral sclerosis and of primary lateral sclerosis, and that amyotrophy may develop in cases of posterolateral sclerosis.[41]

Recent pathologic studies have contributed to a better understanding of the fundamental lesions in amyotrophic lateral sclerosis. In a study of the brains and spinal cords from 37 patients with this condition, Davison [42] found the pyramidal tracts in the spinal cord degenerating in all cases, in the medulla as well in all but 4 cases, in the pons and medulla as well in all but 16 cases and in the peduncles, pons and medulla as well in all but 23 cases. In only 12 cases could degeneration be traced from the large pyramidal cells in the frontal cortex into the brain stem and spinal cord. Moreover, the pathologic changes in the spinal cord and lower portion of the brain stem were old and were characterized by gliosis and the complete absence of many nerve fibers, whereas in the upper part of the brain stem the lesions were younger and were characterized by absence of gliosis and by the presence of fragmenting nerve fibers, easily identified in Marchi and sudan III preparations. Davison concluded that the upper motor neuron may begin to degenerate anywhere along its course, but chiefly in the brain stem and spinal cord. He pointed out that these general observations were noted some years ago, but had apparently been forgotten.

Davison's observations do not support the widely held belief that in amyotrophic lateral sclerosis degeneration starts in the motor cortex and proceeds down the pyramidal tracts. On the contrary, they suggest that degeneration begins in the most caudal part of the pyramidal tract and proceeds centralward, so that only in the most severe cases is the entire tract involved, and then much less in the upper than in the lower part of the brain stem. The clinical findings in the present study are in accord with such a concept, inasmuch as the signs of pyramidal tract disease appeared first in the legs and later in higher levels.

Pathologic studies in clinical instances of primary lateral sclerosis by Spiller [9] and in cases of posterolateral sclerosis by Russell, Batten and Collier [43] revealed similar changes in the pyramidal tracts. In addition to lesions in the pyramidal tracts, degeneration has also been noted

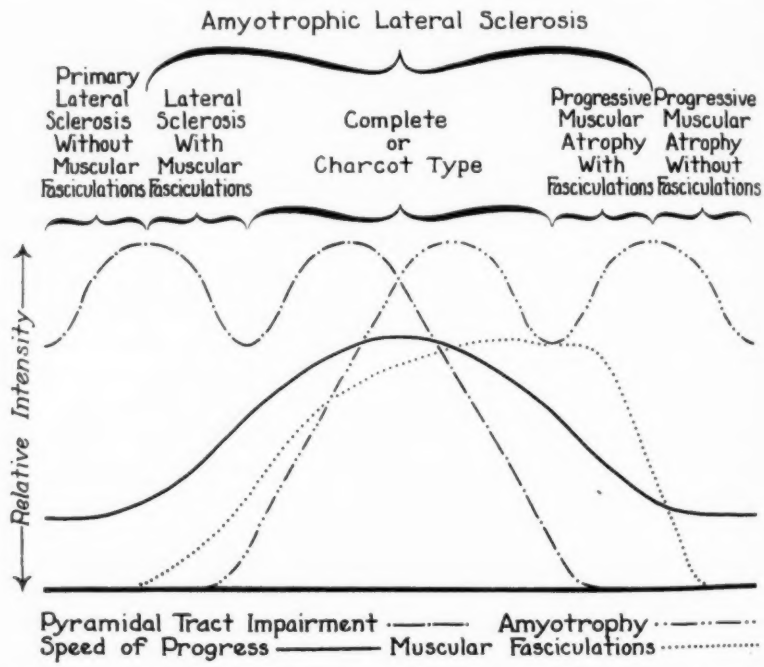
41. Hassin, G. B.: Amyotrophic Lateral Sclerosis Complicated by Subacute Combined Degeneration of Cord: Clinical and Pathologic Report of Case, Arch. Neurol. & Psychiat. **29**:125-138 (Jan.) 1933.

42. Davison, C.: Amyotrophic Lateral Sclerosis: Origin and Extent of the Upper Motor Neuron Lesion, Arch. Neurol. & Psychiat. **46**:1039 (Dec.) 1941.

43. Russell, J. S. R.; Batten, F. E., and Collier, J.: Subacute Combined Degeneration of the Spinal Cord, Brain **23**:39-110. 1900.

in the rubrospinal,[44] spinocerebellar [42] and spinothalamic [42] tracts in cases of amyotrophic lateral sclerosis, the relative infrequency of the spinothalamic changes suggesting that they develop later. It is quite possible that the subjective and later objective sensory alterations in a few of these cases are due to degeneration of the spinothalamic tracts.

By means of fiber analysis, Wohlfart and Swank [10c] demonstrated that large nerve fibers in the ventral spinal roots degenerated first in cases of amyotrophic lateral sclerosis, leaving the small fibers relatively intact. The large ventral horn nerve cells suffered a similar fate, the



Schematic representation of the spectral relationship of the clinical features of the conditions analyzed in this study. Note the reciprocal relationship of amyotrophy and evidences of impairment of the pyramidal tract. Note, also, the close correlation of muscular fibrillations and the speed of progress of the disease.

small cells remaining relatively unharmed. The large fibers in the corticospinal tract areas of the spinal cord also appeared to suffer most in this condition, but accurate measurements of these fibers were impossible, owing to the presence of glial tissue. The inference from this study is that an orderly sequence of degeneration, based on fiber size, occurs in the ventral roots and corticospinal tracts in cases of amyotrophic lateral

44. (*a*) Kuré, K.: Die vierfache Muskelinnervation, Berlin, Urban & Schwarzenberg, 1931. (*b*) Wohlfart and Swank.[10c]

sclerosis; the large fibers degenerate first, and progressively smaller fibers degenerate subsequently. Similar suggestions were made previous to this by Kuré [41a] and Hechst,[45] but their observations were limited and were not supported by measurements.

The observations of Grund [46] and Shelden and Woltman [47] indicate that, contrary to prevailing opinion, the impulses which provoke fascicular twitchings in patients with amyotrophic lateral sclerosis may arise outside the cell body. These investigators blocked the nerve supply of fibrillating muscles with procaine at a point near the spinal cord and observed that the fibrillations continued even though the muscle was completely paralyzed. Further investigation along this line [47a] has corroborated these observations and has shown in addition that injection into a nerve trunk near the muscle it supplies may stop or diminish the fibrillations in most instances, but that sometimes it is necessary to inject procaine directly into the muscle to stop them entirely. These studies suggest that the impulses causing fasciculations arise in the nerve near the muscle, or possibly in the muscle itself in some cases, rather than in the cell body. Furthermore, it suggests that the degenerative changes in the peripheral motor nerves are appearing first in the distal part of the nerve fiber, and not in the cell body. The observation of Denny-Brown and Pennybacker [18] that fasciculations continue in antagonistic muscles during voluntary movement does not appear to conflict with this conception.

Degeneration, according to this pattern, has been shown to occur in cases of thiamine deficiency by Swank [48] and Swank and Prados.[49] In this condition degeneration usually first appears in the distal part of a neuronal process and subsequently progresses toward the cell body. The cell body exhibits the axon reaction later, or in many instances not at all. It is of considerable interest that large fibers degenerate first both in thiamine deficiency and in amyotrophic lateral sclerosis, but in the former condition the proprioceptive sensory fibers are affected first, and in the latter, the large motor nerve fibers. In alcoholic patients it has also been

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45. Hechst, B.: Zur Pathohistologie und Pathogenese der amyotrophischen Lateralsklerose, Arch. f. Psychiat. **93**:159-181, 1931.

46. Grund, G.: Ueber die Entstehung der fibrillären Muskelzuckungen bei spinalen Amyotrophien, Deutsche Ztschr. f. Nervenh. **145**:99-109, 1938.

47. Shelden, C. H., and Woltman, H. W.: Origin of Fibrillary Twitchings, Proc. Staff Meet., Mayo Clin. **15**:646-648, 1940.

47a. Work in progress, with the collaboration of Dr. J. C. Price, of the Neurological Institute of New York.

48. Swank, R. L.: Avian Thiamin Deficiency: Correlation of Pathology and Clinical Behavior, J. Exper. Med. **71**:683-702, 1940.

49. Swank, R. L., and Prados, M.: Avian Thiamin Deficiency: II. Pathological Changes in the Brain and Cranial Nerves (Especially the Vestibular) and Their Relationship to the Clinical Behavior, Arch. Neurol. & Psychiat. **47**:97-131 (Jan.) 1942.

shown by Greenfield and Carmichael [50] that the large nerve fibers in the peripheral nerves suffer the greatest damage. These facts suggest that in some fundamental way the metabolism of motor neurons differs from that of sensory neurons.

It was indicated earlier in this paper that therapy of amyotrophic lateral sclerosis with vitamin E or vitamin B_6 had not been wholly satisfactory. A possible explanation for a few of the optimistic reports has already been offered, namely, that in a few untreated patients the course of the disease is prolonged. All other methods of treatment, to date, have been equally ineffective in altering the course of this disease, with several possible exceptions. Patients with marked bulbar palsy may be greatly improved, although only temporarily, by tube feeding. This improves the general condition of the patient and lessens the incidence of aspiration pneumonia. Also, patients with coincidental cardiac failure, chronic sepsis and similar maladies are frequently greatly benefited by improvement in these superimposed burdens. The hope that amyotrophic lateral sclerosis will respond to specific therapy should not be abandoned, however, in view of the irregular course of the disease in some cases.

SUMMARY

The records of 197 patients with amyotrophic lateral sclerosis, primary lateral sclerosis or progressive muscular atrophy (various types) are analyzed and classified on the basis of their chief clinical manifestations, namely, lateral sclerosis, amyotrophy and muscular fascicular twitchings.

The cases of amyotrophic lateral sclerosis were broken down into three chief types: the Charcot, or completely developed; the atypical, and the incompletely developed. The large majority of the cases were of the first type. They were the typical cases and were characterized by well developed amyotrophy, muscular fasciculations and pyramidal tract signs. The second, or atypical, type included the so-called monoplegic, hemiplegic, lumbar and proximal forms. Each of these terms refers primarily to the distribution of the amyotrophy, degeneration of the pyramidal tracts being essentially the same in all. In most of the cases of the atypical type the amyotrophy eventually developed in other extremities and the clinical picture became complete.

The cases of incompletely developed amyotrophic lateral sclerosis were characterized by predominance of lateral sclerosis, amyotrophy or bulbar palsy. The patients with lateral sclerosis presented rapidly developing pyramidal tract disease with urgency of urination and muscular fibrillations (but no atrophy). The patients with amyotrophy alone pre-

50. Greenfield, J. G., and Carmichael, E. A.: The Peripheral Nerves in Cases of Subacute Combined Degeneration of Cord, Brain **58**:483-491, 1935.

sented rapidly developing muscular atrophy with many muscular fibrillations, and the patients with bulbar palsy showed little besides the bulbar amyotrophy.

In cases of amyotrophic lateral sclerosis there appeared to be a close correlation of the number of muscular fibrillations and the speed of progress of the disease. It should be remembered, however, that the fibrillations may vary from time to time. Elevation of the cerebrospinal fluid proteins seemed to accompany severe amyotrophy, but did not necessarily indicate its rapid progression. Urgency of urination reflected rapid advancement of the pyramidal tract involvement.

Degeneration of the pyramidal tracts was indicated first by hyperreflexia in the legs and later in the arms, then by a Babinski sign and, finally, by absence of abdominal reflexes. Bulbar involvement was usually indicated by amyotrophy first of the muscles supplied by the twelfth cranial nerve, then of the muscles supplied by the ninth and tenth nerves and the lower part of the seventh nerve, and, finally, of the muscles innervated by the masticator division of the fifth nerve. Pains of varying character were common and were often an early symptom, but objective sensory changes were rarely observed.

Primary lateral sclerosis and progressive muscular atrophy, both without muscular fibrillations, ran a course similar in many ways to that of amyotrophic lateral sclerosis, except that it was more slowly progressive. It is suggested that the patients with slowly progressive muscular atrophy without muscular fasciculations were suffering from an arrested or a slowly progressive type of amyotrophic lateral sclerosis, approximately 10 per cent of the cases falling into this group. The reasons for and against this concept are presented, but the absence of suitable pathologic data precludes settlement of the problem at present. Data are also presented which suggest that an occasional patient with the clinical picture of amyotrophic lateral sclerosis recovers.

Miss Sadie Shapiro, of the Social Service Department of the Neurological Institute of New York, assisted in following up patients after discharge.

Fifth General Hospital, United States Army, A. P. O. 1001, % Postmaster, New York.

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HISTOGENESIS OF THE EARLY LESIONS OF MULTIPLE SCLEROSIS

I. SIGNIFICANCE OF VASCULAR CHANGES

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CINCINNATI

Putnam and his co-workers [1] were the first to assign a primary role to vascular lesions in the pathogenesis of multiple sclerosis. They succeeded in producing patches of demyelination by the intravenous injection of various substances (e. g., tetanus toxin). The likeness of such lesions to the foci of multiple sclerosis indicated the possibility that the lesions of multiple sclerosis might be produced by a local circulatory disturbance, "apparently of the nature of an obstruction on the venous side." Dow and Berglund [2] analyzed a large number of lesions of multiple sclerosis. They found thrombi only fifteen times in sixty-five blocks carefully examined. Marburg [3] observed that "thrombosis occurs in acute foci of multiple sclerosis more frequently than is generally assumed. . . . Yet, there are many foci in which blood vessels exhibit no changes in their walls and no venous obstruction." [3b]

The object of this paper is to present additional evidence in support of the primary role of vascular lesions in disseminated sclerosis. The majority of investigators have described the condition of the vessels in multiple sclerosis. Most attention has been given to older plaques, which must be considered as glial scar formations. It is worth while

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

1. (*a*) Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591-1596 (Nov. 28) 1931. (*b*) Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:786-790, 1933; (*c*) Evidence of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298-1321 (June) 1937. (*d*) Alexander, L., and Putnam, T. J.: Cerebral Lesions Due to Vascular Occlusion, ibid., to be published.

2. Dow, R., and Berglund, G.: Vascular Pattern of Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **47**:1-18 (Jan.) 1942.

3. Marburg, O.: (*a*) Die sogenannte akute multiple Sklerose (Encephalomyelitis periaxialis scleroticans), Jahrb. f. Psychiat. **27**:213-312, 1906; (*b*) Studies in the Pathology and Pathogenesis of Multiple Sclerosis with Special Reference to Phlebothrombosis and Guiraud's Bodies, J. Neuropath. & Exper. Neurol. **1**: 3-13 (Jan.) 1942.

to emphasize that in these old lesions the tissue has become secondarily changed. On that account they will receive only passing mention here. A study of the first stages of plaque formation would appear to be of greater significance.

MATERIAL AND METHOD

Twenty cases of multiple sclerosis were studied at the neuropathologic laboratory of the Salpêtrière.[4] In 15 cases the whole brain and spinal cord were available; in 5 cases the histologic study was limited to the brain. All cases studied were typical examples of multiple sclerosis from the clinical and pathologic points of view. Histologic examination by the Spielmeyer, Bielschowsky and Holzer methods confirmed in every instance the clinical diagnosis of multiple sclerosis.

For the present study care was taken to reconstruct a picture of the first stages of plaque formation. In order to be able to trace the process from the beginning the histologic analysis was limited to lesions which were not visible to the naked eye. To obtain this material all gross lesions were avoided and sections were prepared from grossly intact areas. The centrum semiovale, boundaries between the cortex and the white matter and the periventricular areas served as fixed points. Sections were stained by the Spielmeyer, Bielschowsky, Holzer, Cajal, Hortega, scarlet red and hematoxylin and eosin technics. For the demonstration of vascular changes Mallory's connective tissue stain and phosphotungstic acid hematoxylin were used.

RESULTS

Changes in the Myelin Sheaths.—In all cases the loss of myelin was the cardinal feature of the histologic picture. There was an enormous variety in size, shape, demarcation and number of the demyelinated plaques. The usual type described in most textbooks as a more or less sharply circumscribed lesion entirely devoid of myelin was not observed frequently in my material. Such lesions existed in these cases, but they were common only among the older and larger plaques. Their analysis and description are of no interest for the present purpose and are therefore omitted. In many cases areas of demyelination were observed in which the myelin was only partially altered. These areas represented the so-called myelin shadow plaques (Spielmeyer, Steiner) and were distinguished from the completely demyelinated lesions by (*a*) their dark gray color, (*b*) the preservation of numerous beaded and thin myelin sheaths, (*c*) their irregular margins, imperceptibly fading out into the surrounding normal tissue, and (*d*) their relatively small content of lipoid products (scarlet red).

The majority of the small areas of demyelination were perivascular. Their relation to the vascular system is illustrated in figure 1 *A* and *B*. Under low magnification these areas of perivascular demyelination

4. Professor Guillain and Dr. Ivan Bertrand gave me permission to use this material.

appeared as light-staining circular or oval zones surrounding small veins and capillaries. Each lesion contained a blood vessel, which was usually so oriented as to be central. In the majority of the lesions the central vessel could be identified as a small vein. The perivascular areas of demyelination revealed the following characteristic changes in the myelin sheaths: In the central part of the plaque the destruction of myelin was generally complete, practically no or very few fragments being discernible (fig. 1 *A*). At the periphery a transitional zone was often observed, characterized by swelling, fragmentation and beading of the myelin sheaths. This zone, however, was sometimes very small or imperceptible, so that the transition between destroyed and normal myelin was rather abrupt, the demyelinated lesions being sharply defined. As a rule an

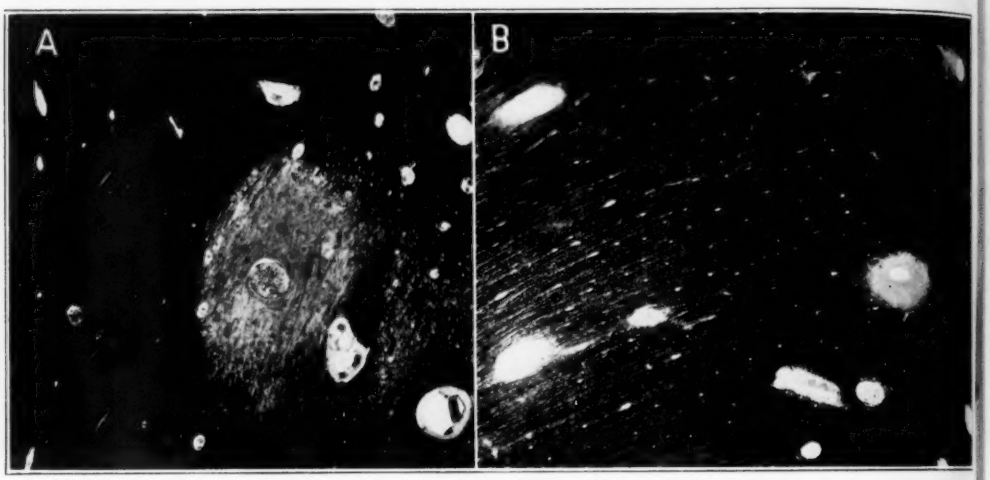

Fig. 1.—*A*, an "early" perivascular plaque about an obstructed blood vessel; × 80. *B*, circular or oval zones of demyelination surrounding small blood vessels; × 70. Spielmeyer myelin sheath stain.

intermediate zone lay between the necrotic center and the marginal portion of the lesion, in which the myelin sheaths stained lightly and were often thin and beaded.

Changes in the Axis-Cylinders.—Spielmeyer and Bielschowsky preparations were made of adjacent sections from the same block of tissue. In general it appeared that all plaques could be divided in three types: (1) those in which the axis-cylinders were completely destroyed and practically absent; (2) those in which the axis-cylinders were severely damaged and reduced in number, and, finally, (3) those in which the axis-cylinders were fairly well preserved or substantially intact. It appeared that the last type of lesion was the most common among the

small perivascular patches. In some of the plaques no definite diminution in number of axis-cylinders could be observed. Sometimes, however, in the center the axis-cylinders were fragmented and degenerated and slightly decreased in number, whereas in the periphery they appeared to be substantially intact. In general, it can be said that the destruction was less noticeable as one passed from the center to the periphery of the lesion. In many of the smallest perivascular plaques there was extreme tumefaction of the axis-cylinders. Presumably this axonal swelling represents one of the earliest changes, and one which may be reversible.

Changes in the Glia.—In the majority of descriptions of the histologic changes in multiple sclerosis the early glial changes have not been stressed. They may, therefore, be described in detail. Three types of glial reaction were observed. There was pronounced rarefaction and a spongy appearance of the glial reticulum, with loss of affinity for the stain. In many small plaques the tissue contained numerous vacuoles, some of which harbored myelophages and gitter cells. Many of the plaques were traversed by preexistent glia fibers, which in some instances were torn by the distended vacuoles. Similar changes were first described by Redlich [5] as a predominant feature of early plaque formation. Borst [6] interpreted these changes as due to lymph stagnation (so-called *Hyperlymphose*). Steiner [7] described them as *circumfocale Arcolierung* and observed this type of glial change mostly in the tissues surrounding the plaques. In Cajal and Holzer preparations the neuroglia appeared degenerated in the central part of the lesion. At the periphery some degenerated astrocytes could be seen; their cytoplasm was swollen and their dendrites were broken. In some lesions there was a slight increase of connective tissue, seemingly originating from the blood vessel walls.

In some of the patches Hortega preparations revealed numerous microglia cells with the most bizarre nuclei, most of which were bean shaped or kidney shaped. At the periphery of the foci various phases of transformation of the microglia into compound granular cells could be observed. Some of the patches contained numerous gitter cells, which were associated with occasional gemästete cells and with many myelophages. Astrocytes were rarely observed and were usually present only in the marginal areas of the patches. In some regions gemästete cells attained enormous dimensions and appeared as monster cells.

Glial fibrosis in the form of scars was only occasionally observed. In such areas in which the glial reaction was especially active prolifera-

5. Redlich, E.: Ueber multiple Sclerosis, Deutsche Klin. **6**:557-587, 1906.

6. Borst: Die multiple sklerose des Zentralnervensystems, Ergebn. d. allg. Path. u. path. Anat. **9**:67-187, 1903-1904.

7. Steiner, G.: Krankheitserreger und Gewebsbefund bei multipler Sklerose, Berlin, Julius Springer, 1931.

tion of astrocytes was conspicuous. Comparison of this type of glial reaction with that described in older lesions showed no structural differences. A more detailed description of them is therefore omitted.

Vascular Changes.—The relation of the vascular system to the lesions has been mentioned and is illustrated in figure 1. In about two thirds of all early lesions stained by the Spielmeyer method, the patches were in the form of circular or oval demyelinated plaques which surrounded medium-sized veins or capillaries. Most of the blood vessels within the

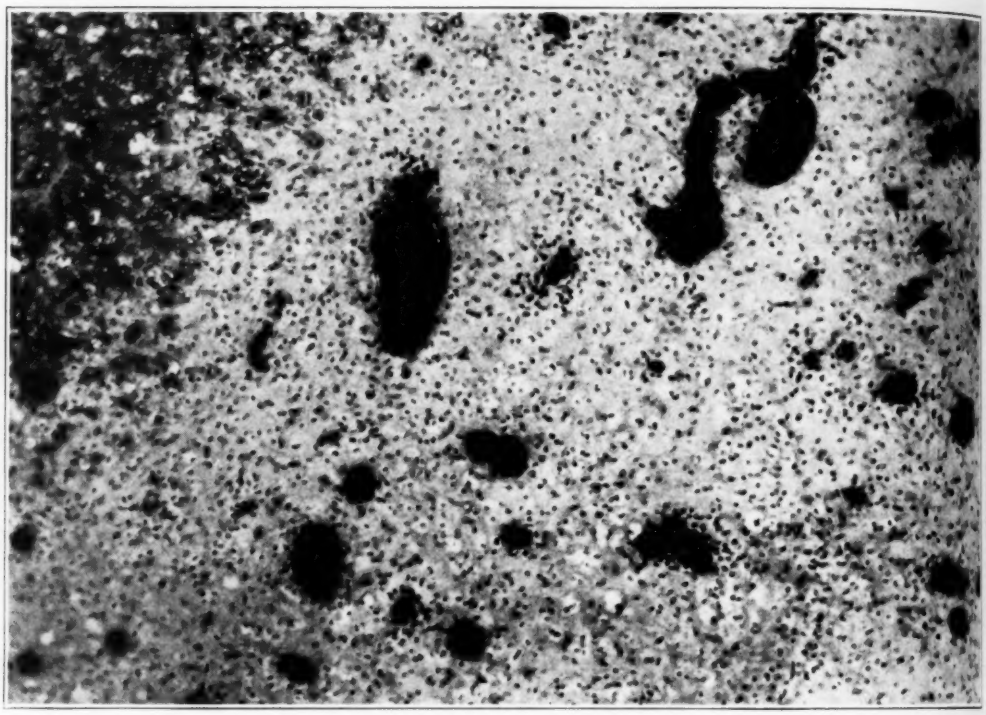

Fig. 2.—Marked dilatation, engorgement and stasis of the small blood vessels in a demyelinated area. Spielmeyer myelin sheath stain; × 110.

lesions revealed marked dilatation and enormous engorgement with blood (fig. 1 *A*). In some of the larger lesions the vascular engorgement and stasis were especially striking (figs. 2 and 3 *A* and *B*). The small veins and capillaries were enormously distended and showed some tortuosity and beadlike dilatations.

The presence of vascular occlusion and thrombus formation was not always easy to identify. Clots of agglutinated red blood cells were frequently observed. The individual red blood cells were usually fused

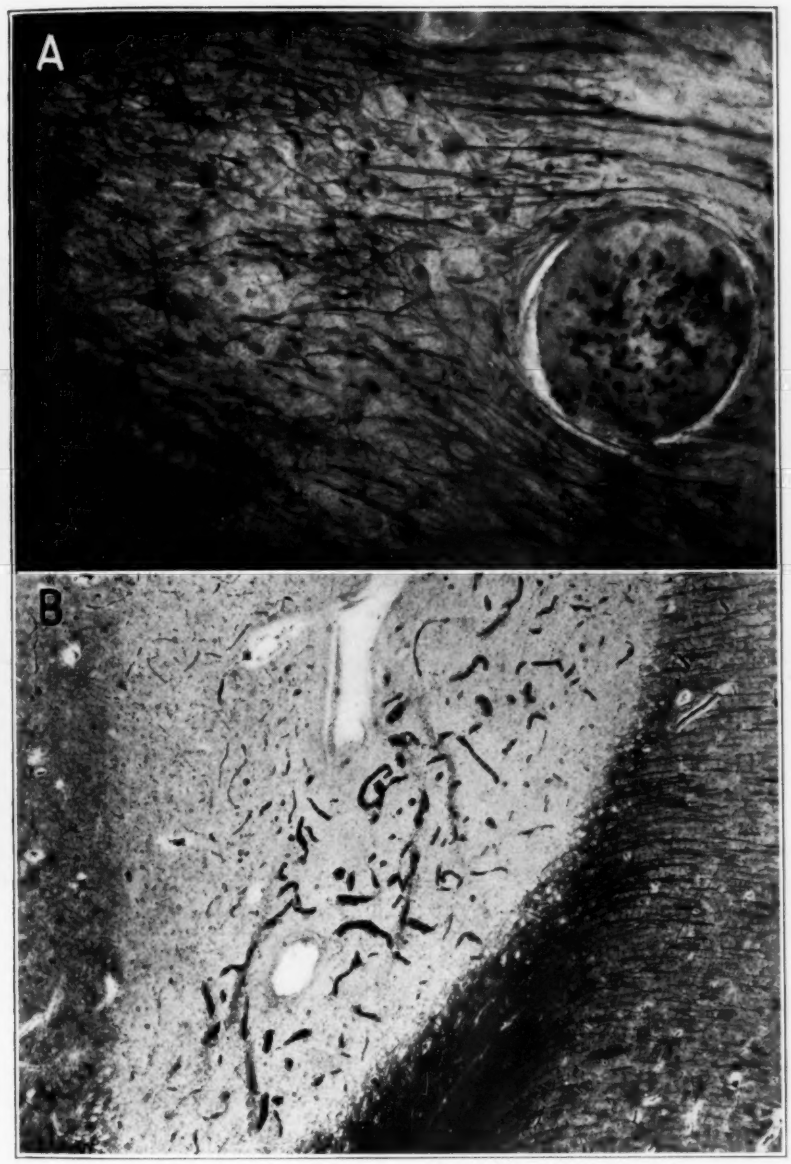

Fig. 3.—*A*, perivascular loss of myelin sheaths; complete filling of the central blood vessel with agglutinated platelets, fibrin and pigment. × 125. *B*, vascular engorgement and stasis of the small blood vessels in a larger area of demyelination. × 125. Spielmeyer myelin sheath stain.

together and formed an amorphous mass. In some areas the occlusive changes consisted of complete filling of the vascular channel with large masses of agglutinated platelets, broken-down blood corpuscles and a few strands of freshly formed fibrin and pigment (fig. 3 *A*). More striking occlusive changes are illustrated in figure 4 *A*. They consisted of complete filling of the lumen of the blood vessel by a solid plug of agglutinated blood mixed with an unusually heavy deposit of strands of fibrin curved toward the vessel wall. Occasionally an early stage of organization was associated with degenerative changes of the vessel wall (fig. 4 *B*). In addition to these vascular changes, perivascular hemor-

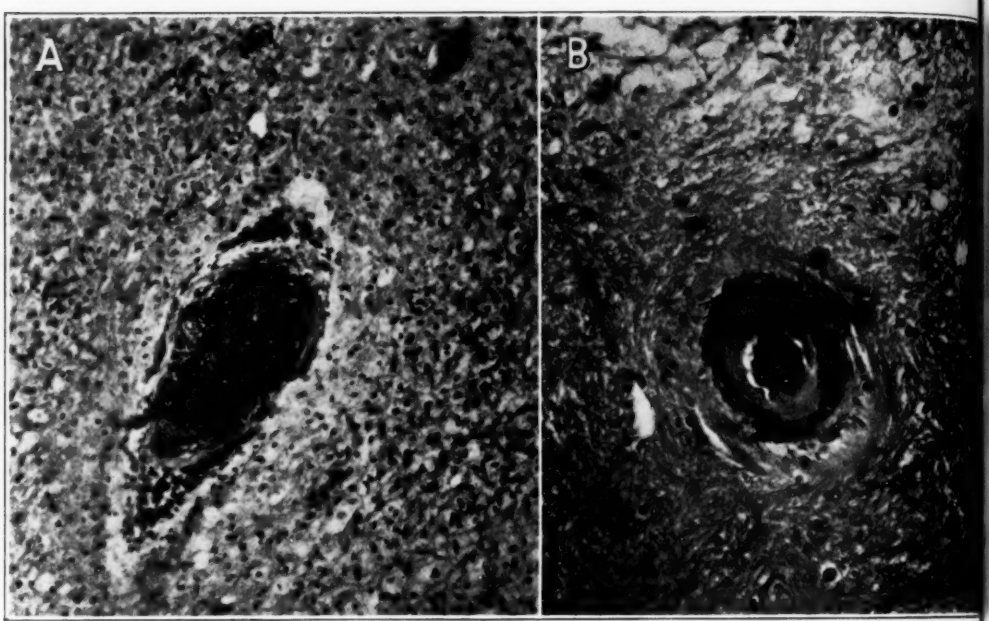

Fig. 4.—*A*, completely occluded blood vessel in the central area of a demyelinated plaque, showing solid plug of agglutinated blood mixed with strands of fibrin adherent to the wall of the vessel. *B*, a blood vessel in the vicinity of a plaque completely occluded by a partly organized thrombus. Hematoxylin and Van Gieson stain; × 135.

rhages and deposits of yellow pigment were often observed in the distended perivascular spaces.

Perivascular Infiltration and Inflammatory Phenomena.—In about one third of the cases perivascular accumulation of cells was observed. In some cases the majority of the perivascular cells could be identified as fat granule bodies. Others were rod cells. Further, proliferation of astrocytes within the perivascular tissue was fairly constant. Accumula-

tions of lymphocytes were seldom observed. There was a marked variation in the content of lymphocytic infiltration not only from case to case but from lesion to lesion in the same case. In general, it appeared in this series of cases that lymphocytic infiltration was an infrequent occurrence.

COMMENT

This study has demonstrated rather strikingly the frequent association of the early lesions of multiple sclerosis and vascular disturbances. The latter consisted of thrombosis of small veins and dilatation, engorgement and stasis of the capillaries and veins. The great majority of small lesions have been observed to be oriented about small veins. The question inevitably arises why vascular disturbances, which can be considered as of frequent occurrence in small and recent plaques, are relatively infrequent in the large and older lesions.

Two factors appear to be of importance: 1. In elongated lesions containing central veins the patches never tend to follow the entire course of the blood vessel.[8] In the great majority of instances only one circumscribed area of the plaque is connected with the blood vessel. The foci usually envelop the central vein for a short and limited distance. As the lesion becomes larger the relation with the primary blood vessel becomes less evident. The demyelinated area tends to progress diffusely into the nerve parenchyma in different directions independent of the distribution of the primary blood vessel. It is not surprising, therefore, that in many sections from a large lesion the primary blood vessel will not be found. 2. The presence or absence of vascular changes in lesions may depend on the duration of the morbid process. Alexander and Putnam [1d] suggested that thrombi of the small veins in the older lesions of multiple sclerosis may disappear without a trace. Certainly, in older sclerotic plaques it is more difficult to trace them than in the recent lesions.

SUMMARY

In 20 cases of multiple sclerosis the early stages of plaque formation and their relation to the vascular system were studied. A positive correlation was found between the early lesion and the presence of vascular abnormality. The view is expressed that vascular change, particularly occlusion by thrombosis, is an essential factor in the pathogenesis of demyelinated plaques.

Cincinnati General Hospital.

8. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **38**:1-15 (July) 1937.

EFFECT ON THE ELECTROENCEPHALOGRAM OF CHANGING THE BLOOD SUGAR LEVEL

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In 1939-1940 electroencephalographic observations and determinations of the blood sugar were made on a group of 43 college undergraduates under standardized conditions. An attempt was made to relate the range of blood sugar levels to the type of the electroencephalographic pattern (Davis [1]), the alpha frequency and the normality rating of the electroencephalogram. No correlation was found. An attempt was also made to relate the electroencephalographic pattern to the responses of the electroencephalogram during three minutes of hyperventilation. The low voltage, fast frequency types of electroencephalograms (beta or mixed fast patterns [1]) appeared to be more resistant to change than the alpha or mixed slow types. Aside from this, there were no consistent observations. It appears that the fasting blood sugar level of a subject has no consistent relation to the electroencephalogram.

In 1940-1941 electroencephalographic observations were made on 40 healthy college students simultaneously with an "insulin tolerance test." [2] The study of the electroencephalographic pattern with a varying blood sugar level is the basis of the present paper.

METHOD

A routine electroencephalogram was recorded for one-half hour between 8 and 9 a. m., while the subject was in a fasting condition; i. e., he had not had food for the previous twelve hours. The routine electroencephalogram included simultaneous records from both sides of the head and the midline of the frontal, the precentral and the occipital region.[1] If asymmetry between the two sides of the head was found, the more normal side was chosen for continuous recording later in the procedure. Insulin (0.05 unit per kilogram of body weight of insulin

† Mrs. Davis died on July 11, 1942.

This work was aided by a grant from the Josiah Macy Jr. Foundation. Through the Grant Study of Harvard University, Dr. Clark Heath and Dr. John Thompson collaborated in the blood sugar determinations.

1. Davis, P. A.: Technique and Evaluation of the Electroencephalogram, J. Neurophysiol. **4**:92, 1941.

2. Csépai, K., and Ernst, Z.: Insulin Susceptibility of the Human Body, Orvosi hetil. **71**:1497, 1927. de Takáts, G.; Fenn, G. K., and Trump, R. A.: Splanchnic Nerve Section in Juvenile Diabetes, Ann. Int. Med. **7**:1201, 1934. Bauer, J., and Mongino, J.: Ueber den Schwellenwert des Insulins, Ztschr. f. klin. Med. **121**:476, 1932.

containing 40 units per cubic centimeter) was then injected intravenously, and from this time for one hour a continuous electroencephalogram and record of the pulse rate were made while the subject was lying comfortably relaxed on a bed with his eyes closed. Between forty-five and fifty minutes after injection of the insulin, 50 cc. of Karo corn syrup (Red Label) in an approximately equal amount of water was given the subject by mouth. Blood, for measurements of the blood sugar,[3] was taken from the finger at two, twenty, twenty-five, thirty, thirty-five and forty-five minutes after the injection of insulin and fifteen minutes after the corn syrup was given. Blood pressure readings were made at approximately five minute intervals. Between fifteen and twenty minutes after the corn syrup was given, when the blood sugar usually approximates its original level, the subject's response to hyperventilation for three minutes was recorded electroencephalographically.

RESULTS

Forty-three observations were carried out on 40 healthy college students, whose ages ranged from 17 to 23 years, with 3 subjects repeating the experiment under the same conditions.

TABLE 1.—*Range in Pulse Rates*

	Beats per Minute
Average pulse rate before injection of insulin	38-76
Highest pulse rate	64-100
Pulse rate at 45 minutes	52-83
Pulse rate 15 minutes after ingestion of Karo corn syrup, approximately 1 hour after insulin	51-78
Acceleration	3-42
Deceleration from peak to 45 minutes	0-39
Deceleration from peak to 1 hour	3-33
Change: Deceleration (27 observations)	0-14
Acceleration (14 observations)	0-16

Blood Sugar.—The fasting blood sugar level varied from 92 to 129 mg. per hundred cubic centimeters. The lowest level, which was reached usually between twenty-five and thirty minutes after injection of insulin, varied from 53 to 85 mg. per hundred cubic centimeters. The blood sugar approached the fasting level at forty-five minutes and reached or exceeded it fifteen minutes after the corn syrup had been taken (76 to 126 mg. per hundred cubic centimeters).

Pulse Rate.—Table 1 gives the range of the pulse rates for these subjects. Changes in pulse rate were not correlated with changes in the electroencephalogram. There was a notable variability of pulse rate before and after the blood sugar level changed. The most rapid change in pulse rate occurred during the first minute of hyperventilation, while the electroencephalogram was still stable.

Blood Pressure.—Changes in blood pressure occurred, but they could not be correlated with electroencephalographic changes.

3. Folin, O., and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115, 1929.

Electroencephalogram.—The electroencephalogram showed a slight shift toward the slow end of the frequency spectrum and increasing instability as the blood sugar level decreased. The transition occurring in response to insulin started as early as ten minutes, but usually not

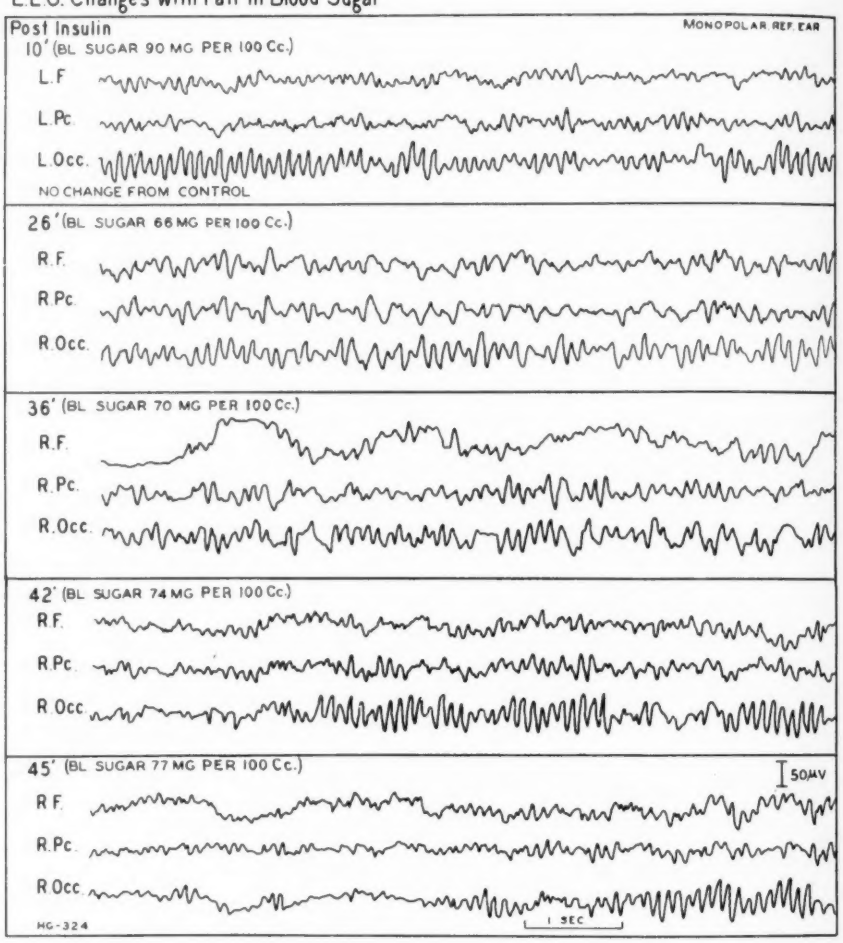

Fig. 1.—Typical electroencephalographic changes occurring with alterations in the level of blood sugar.

until twenty minutes after injection of the drug. The alpha activity became irregular and the per cent time alpha decreased as 8 per second or other slow waves appeared (fig. 1). The precentral record showed this change more clearly, although the base line of the simultaneous frontal record became unstable before the 8 per second waves were clearly developed.

From the thirtieth to the forty-fifth minute in most instances, long slow swings began emerging in the frontal record, usually obscuring the 4 to 8 per second activity (fig. 1). These slow swings were of from two to as long as five seconds' duration (fig. 2). Ultimately they gradually lengthened out until the base line became steady once more. Capacity-coupled amplifiers were employed, so that one could not be sure whether the stabilization was due to cessation of the slow swings or merely to their becoming so slow that they were no longer recorded by the amplifier. The consistency of the appearance of the slow swings made it possible to study their relationship to other factors. Although they

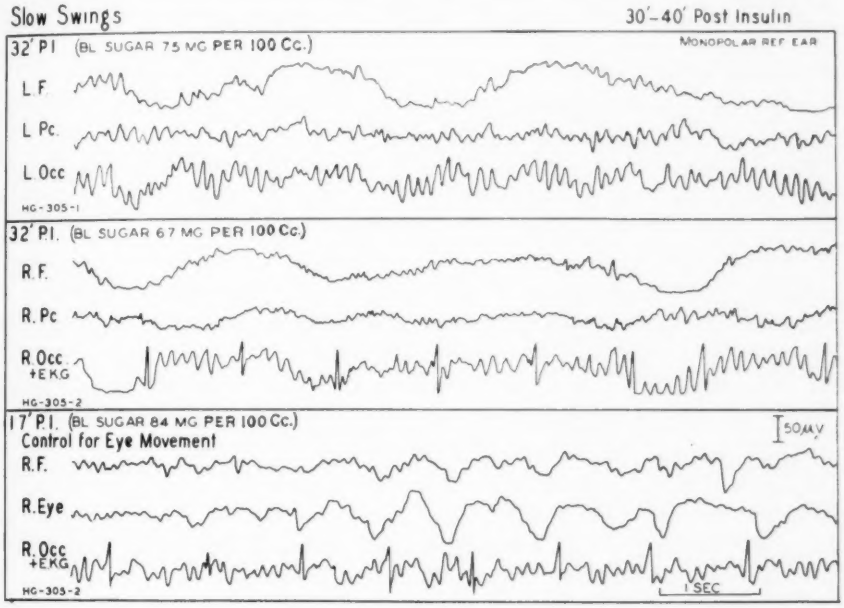

Fig. 2.—Slow swings occurring with alterations in the blood sugar level thirty to forty minutes after insulin and the control for eye movements. Eye movements, registered in the second line of the control sample, produced swings in the frontal record that were of less amplitude and much quicker than the "slow swings" shown in the first two samples. For recording of the pulse rate (second and third samples), one grid of the third amplifier was connected to a potentiometer placed between the electrode from the right ear and an electrode on the wrist. The other grid of this amplifier was connected to an occipital electrode, so that the occipital electroencephalogram and the electrocardiogram appear simultaneously in the record.

appeared most frequently from the frontal lead, they occasionally appeared from the occipital lead, while the record from the precentral lead was usually stable (fig. 2). These slow swings are similar to

those found by Lovell, Czarski and Lyman [4] in experiments on the responses to stimulation of the vestibular mechanisms. These authors proved that the slow swings originated in the skin and were related to disturbances in the autonomic nervous system, as indicated by sweating, pallor and changes in respiration. It is worthy of note that these slow swings in the electroencephalographic record in the frontal and occasionally in the occipital region have been associated with disturbances of the autonomic nervous system, and yet that they have been produced by stimulation of the vestibular mechanisms and also by lowering the blood sugar level by means of injections of insulin. Probably in my subjects the autonomic nervous system was also involved, since the pulse rate generally increases as the blood sugar level reaches its minimum, and my subjects usually showed mild sweating and pallor.

By the forty-fifth minute these slow swings usually disappeared (fig. 1). In a few subjects hyperventilation caused reappearance of these swings for a short time. In 1 subject, who went into partial syncope seven minutes after injection of insulin, all three areas showed these swings. His blood pressure, which had been 104 mm. of mercury systolic and 74 mm. diastolic before insulin was given, fell to 75 mm. systolic and 45 mm. diastolic at the onset of the partial syncope and was 88 mm. systolic and 65 mm. diastolic three minutes later. Thereafter his blood pressure remained stable between 92 mm. systolic and 56 mm. diastolic and 104 mm. systolic and 60 mm. diastolic during the remainder of the experiment, while the long swings reappeared and remained from the twenty-fifth through the fifty-sixth minute. The experiment was repeated with this subject, but the swings did not appear. As electrodes were being put on before the second test, he volunteered the information that he had been inwardly a bit panicky and uncertain about what to expect in the first experiment.

In another subject, these swings appeared thirty-two minutes after injection of insulin in each of 2 experiments. The swings in the frontal record were found to be independent of the changes recorded from an eye lead placed just under and against the eyebrow (fig. 2). Administration of 100 per cent oxygen for approximately five minutes had no apparent effect on these swings.

The electroencephalogram usually remained unstable for from ten to twenty minutes after the level of blood sugar began to rise. The 4 to 8 per second waves became irregular as low voltage, 16 to 20 per second waves occasionally appeared. After this the electroencephalogram gradually resumed its previous character with the return of alpha activity

4. Lovell, H. W.; Czarski, T. J., and Lyman, R. S.: The Effect of Vestibular Stimulation on Brain Waves, Chinese J. Physiol. **14**:389, 1939.

(fig. 1). In all subjects the electroencephalogram was unstable when the lowest point in the blood sugar curve was reached. In some the irregular slow waves increased in voltage and developed into clear "episodes" (fig. 3), which continued to reappear even as long as twenty minutes after the administration of corn syrup.

Hyperventilation for three minutes was carried out after the blood sugar had returned to its normal level. A preliminary demonstration and explanation of hyperventilation were always given. The rate and depth of breathing for each subject were such that he could maintain

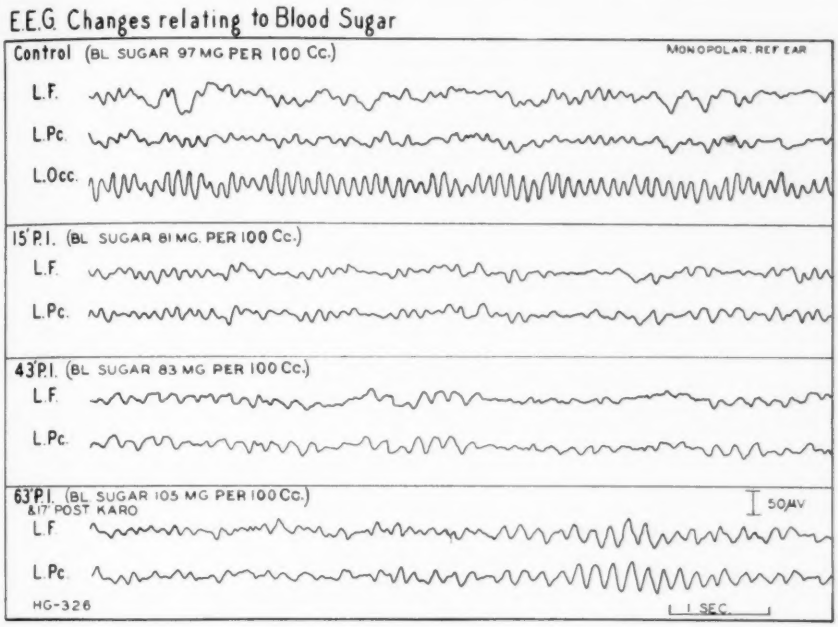

Fig. 3.—Organization of latent dysrhythmia into definite 6 cycle episodes as a result of altering the blood sugar level.

a steady pace at approximately his maximal capacity, with no delay between breaths. In this way an attempt was made to allow for individual differences in respiration by having the subject regulate his own breathing in meeting the requirements of the procedure.

The amount of alteration in the electroencephalogram following the injection of insulin and also on hyperventilation was rather clearly related to the character of the routine electroencephalogram. In general the subjects whose preinsulin records showed indications of slow dysrhythmic activity were the ones in whose records the most dysrhythmia appeared after insulin and the clearest "episodes" of slow waves developed. The records that were initially the most stable and regular,

or revealed faster than average alpha waves, and were freest from slow waves showed the least change after insulin or during hyperventilation.

All of the routine records were typed—alpha (*A*), beta (*B*), mixed fast (*MF*), mixed (*M*) and mixed slow (*MS*)—and rated for "normality" (1, 2, 3, 4 and 5) according to the criteria described elsewhere.[1] They were also examined specifically for the presence of slow waves, either as definite episodes or as diffuse dysrhythmia. They were then judged independently (by Mrs. S. R. Blake) for the prominence of slow waves appearing after insulin and during hyperventilation. In table 2 the data are arranged in groups in order of diminishing promi-

TABLE 2.—*Classification of and Data on Electroencephalograms of Forty Healthy Subjects* *

Electroencephalogram No.	Relative Prominence of Slow Waves: Routine	After Insulin	After Hyperventilation	Lowest Blood Sugar Level, Mg. per 100 Cc.	Type of Electroencephalogram	Alpha Frequency	"Normality Rating"
300	+++	+++	+++	76	M	10	4
303	+++	+++	+++	71	M	10.5	4
317	+++	+++	++	69	M	10+	4
325	+++	++	+	62	MS	8-10	4
306	++	+++	+++	59	MS	9	4
301	++	++	++	74	M	10	3+
324†	++	++	+	60	M	9.5-10	3+
338	++	++	—	77	M	10-11	4
343	++	++	—	76	B	11	3
311	++	—	++	65	M	10	3+
350	++	—	—	62	B	10-11	3+
326†	+	+++	+++	68	A	9-9.5	2+
302	+	+++	—	74	A	9-10	3+
272	—	++	++	53	A	9-10	3
275	+	++	+	57	MF	11	3
349	+	+	++	69	MS	9-10	3
347	+	+	—	81	MS	9.5-10	3+
348	+	+	—	70	B	10 —	3
305†	+	+	—	72	A	10	3
346	+	+	—	67	MS	10	2+
342	+	—	+	85	MS	10	2+
341	—	++	—	77	MS	9.5-10	3+
310	—	+	—	62	M	11	2+
336	—	+		64	MF	11-12	2+
329	—	+	—	67	A	10	2+
315	—	—	++	62	M	10	3
337	—	—	+	74	M	9-10	3+
345	—	—	+	71	M	9-9.5	3
304	—	—	+	68	A	11	2+
314	—	—	+	62	A	10	2+
344	—	—	+	76	MF	10-11	2
335	—	—	—	67	A	10	3+
334	—	—	—	62	MF	11	3+
309	—	—	—	66	A	10	2+
333	—	—	—	69	A	10 —	2+
323	—	—	—	55	MF	10-11	2+
340	—	—	—	57	MF	11	2+
332	—	—	—	72	MF	10-11	2+
328	—	—	—	68	MF	10-10.5	2
331	—	—	—	65	A	9.5-10	2

* The prominence of slow waves was judged on a relative scale (+++, ++, + and —) for each test separately, although the absolute voltage and prominence of slow waves were much greater under the influence of insulin and hyperventilation than in the routine record. For full definition of types of electroencephalograms see Davis.[1] A indicates regular alpha pattern; M, mixed pattern, with alpha activity plus faster and slower waves; MF, mixed fast pattern, with alpha activity and faster waves; MS, mixed slow pattern, with alpha activity and slower waves, and B, low voltage (beta) pattern. The "normality rating" scale extends from 1 (most regular and normal) to 5 (abnormal dysrhythmia).

† These records are illustrated in figures 1, 2 and 3.

nence of slow waves in the routine records and, within each group, according to the reaction to insulin and to hyperventilation. The general correspondence (and also the occasional divergences) in rating according to the various criteria are evident.

COMMENT

It seems clear that neither insulin nor hyperventilation induces dysrhythmia equally in all electroencephalographic records. Both the fall in blood sugar and the hyperventilation apparently accentuate preexisting dysrhythmic tendencies and make them more evident to casual inspection. Davis and Wallace [5] pointed out the synergistic action of a low blood sugar level and of hyperventilation in producing slow waves and the stabilizing effect of a high blood sugar level in the presence of hyperventilation. The present observations further emphasize the close relationship of the electroencephalographic reactions to low blood sugar and to hyperventilation, and also the dependence of both reactions on individual differences revealed by careful examination of the routine electroencephalogram.

The relation of the electroencephalographic changes during hyperventilation to the type of the electroencephalogram is particularly clear (table 2). None of the 3 subjects with records of the low voltage (beta) type and only 1 of the 8 subjects with tracings of the mixed fast type showed clear, slow waves, while nearly all with the mixed and mixed slow types showed them more or less prominently. The subjects with alpha patterns formed an intermediate group, of whom some did and some did not show positive reactions. My (unpublished) observations on an earlier (1939-1940) group of students showed this same stability of the beta and the mixed fast type during hyperventilation. In still another set of experiments (unpublished), carried out in collaboration with Dr. A. Graybiel, in which the rate of breathing was set for all subjects and the tidal volume measured and controlled on the basis of body weight, the results were the same.

Both the insulin test and the voluntary hyperventilation apparently serve to accentuate characteristics that are present, but less clearly evident, in the routine electroencephalogram. The alteration of the blood sugar level, although more time consuming, has the advantage that it does not require the intelligent, active cooperation of the subject and may therefore be applicable in certain cases in which the subject is uncooperative or unintelligent and the hyperventilation test is unsatisfactory or impractical.

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5. Davis, H., and Wallace, W.: Factors Affecting Changes Produced in Electroencephalogram by Standardized Hyperventilation, Arch. Neurol. & Psychiat. **47**:606 (April) 1942.

All the subjects for these tests were normal healthy college sudents. It would be of interest to determine the effect of the insulin test on the electroencephalograms of abnormal subjects, particularly of known epileptic patients.

SUMMARY

Electroencephalograms were recorded on 40 healthy college students (*a*) during a routine rest period, (*b*) for forty-five minutes after intravenous injection of insulin (0.05 unit per kilogram of insulin containing 40 units per cubic centimeter), (*c*) for fifteen minutes thereafter after oral ingestion of 50 cc. of Karo corn syrup and, finally, (*d*) for three minutes of voluntary hyperventilation. The blood sugar level, the pulse rate and the blood pressure were determined systematically.

No consistent relation appeared between the electroencephalographic changes and the pulse rate or the blood pressure.

As the blood sugar level fell (to a minimum of 53 to 85 mg. per hundred cubic centimeters), the normal alpha activity of the electroencephalogram was increasingly replaced by slower waves, chiefly in the 6 to 8 cycle range. The electroencephalogram returned to normal with the restoration of the blood sugar level, but electroencephalographic changes lagged ten minutes or more behind the changes in the blood sugar.

"Slow swings," of two to five seconds' duration, often appeared in the frontal record during the height of the insulin reaction. These potential changes apparently originate in the skin of the forehead.

The appearance of conspicuous electroencephalographic changes during the insulin test correlates fairly closely with the appearance of prominent slow waves during hyperventilation and with the presence of (much less prominent) slow waves in the routine electroencephalogram. Marked electroencephalographic changes during both tests were common in the mixed and the mixed slow type of electroencephalogram, less common in the regular alpha type and rare in the low voltage and the mixed fast types.

The relative advantages of the insulin and the hyperventilation test for revealing latent electroencephalographic characteristics are considered.

RESULTS OF INSULIN AND EPINEPHRINE TOLERANCE TESTS IN SCHIZOPHRENIC PATIENTS AND IN NORMAL SUBJECTS

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Recent investigations on carbohydrate metabolism for use in diagnosis of endocrinopathies [1] have provoked interest in their possible application to the problem of schizophrenia. Horvath and Friedman [2] reported that after the intravenous administration of insulin schizophrenic patients showed a delay in the hypoglycemic effect and the subsequent recovery as compared with normal subjects. Meduna, Gerty and Urse [3] found an anti-insulin factor to be present in the blood of schizophrenic patients which was specific for that psychosis. Gellhorn, Feldman and Allen [4] using the hypophysectomized-adrenomedullated rat as an assay object, obtained results somewhat contrary to those noted by these authors. The latter stated that there was no difference in the insulin content of the blood of normal and of psychotic subjects, in a quiet state. Under the stress of excitement, however, the blood insulin of psychotic (including schizophrenic) patients so increased as to have a hypoglycemic effect, a phenomenon which was never seen in excited normal subjects.

From the Memorial Foundation for Neuro-Endocrine Research and the Research Service of the Worcester State Hospital.

1. Fraser, R.; Albright, F., and Smith, P. H.: The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose-Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism, J. Clin. Endocrinol. **4**:297, 1941.

2. Horvath, S. M., and Friedman, E.: The Effects of Large Doses of Intravenous Insulin in Psychotic Nondiabetic Patients, J. Clin. Endocrinol. **1**:960, 1941.

3. Meduna, L. J.; Gerty, F. J., and Urse, V. G.: Biochemical Disturbances in Mental Disorders: I. Anti-Insulin Effect of Blood in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **47**:38 (Jan.) 1942.

4. Gellhorn, E.; Feldman, J., and Allen, A.: Effect of Emotional Excitement on the Insulin Content of the Blood: Contribution to Physiology of Psychoses, Arch. Neurol. & Psychiat. **47**:234 (Feb.) 1942.

The present study was designed to investigate the glycemic and cardiovascular effects of insulin and epinephrine with the technics suggested by Fraser, Albright and Smith.[1] It was carried out on 32 male schizophrenic patients with no evidence of physical disease and on 20 normal men.

All subjects were studied in a fasting state, reclining quietly in bed throughout the period of the test. After a preliminary venipuncture for determination of the fasting blood sugar, insulin was injected intravenously in amounts of 0.1 unit per kilogram of body weight. The blood sugar was then determined at half-hour intervals for the next two hours. Immediately subsequent to the last venipuncture, epinephrine hydrochloride (1 : 1,000) was injected intramuscularly in amounts of 0.01 cc. per kilogram of body weight. Samples of blood were again taken thirty and sixty minutes later. Before each venipuncture the blood pressure and the pulse rate were measured to determine the possible effects of the substances on the autonomic nervous system. The patients and half of the normal subjects lived on the routine hospital diet, which was rather high in carbohydrate. The other 10 normal subjects lived outside the hospital and may have had a somewhat different diet. All blood sugars were measured by a single person, the Folin-Wu technic (alkaline tartrate colorimetric method) being used.

The ages of the patients ranged from 15 to 46 years, the average being 30 years. They had been confined to the hospital from four days to fifteen years at the time of the test, the mean period being four years. Nineteen subjects had been hospitalized for less than one year. The diagnoses included all the recognized subtypes of schizophrenia. The normal subjects were somewhat younger than the patients, their ages ranging from 17 to 31 years, with an average of 24 years. This difference in age between the two groups, however, is of no importance from the physiologic point of view.

The mean values for the blood sugars obtained during the study are shown in table 1. The control figures were essentially the same for the two groups, the difference of 3 mg. being insignificant. A half-hour after the injection of insulin the mean for the normal subjects decreased to a level of 29.6 mg. per hundred cubic centimeters, while the corresponding value for the patients was 39.2 mg. per hundred cubic centimeters.[5] One hour after the injection the mean values were 61.1 mg. for the normal subjects and 63.6 mg. for the patients. The difference

5. For another group of 17 schizophrenic patients whose blood sugars were measured by a different technician (Miss Anne Walsh), the mean value thirty minutes after injection of insulin was 51.3 mg. per hundred cubic centimeters, a result which corroborates to an even greater degree the differences already cited.

between the two groups had been reduced from 9.6 mg., in the previous reading, to 2.5 mg. This seems to indicate that the phase of recovery from the hypoglycemic level was more active in the normal subjects. During the next hour the values for the two groups were essentially similar. Up to this point, then, the trend indicates a greater resistance to insulin, and possibly a less rapid recovery from the hypoglycemic phase, of the patients. As the recovery from the hypoglycemia is presumably due, at least in part, to endogenous adrenomedullary activity,[6] with subsequent mobilization of sugar into the blood stream, this observation is of interest as compared with the results obtained after epinephrine was injected. The levels of blood sugar two hours after the injection of insulin, although not quite back to the original values, were

TABLE 1.—*Means of Values for Blood Sugar, Blood Pressure and Pulse Rate of Twenty Normal and Thirty-Two Schizophrenic Subjects Obtained During the Course of Insulin and Epinephrine Tolerance Tests*

		After Insulin				After Epinephrine	
	Fasting	0.5 Hr.	1 Hr.	1.5 Hr.	2 Hr.	0.5 Hr.	1 Hr.
Blood sugar (mg. per 100 cc.)							
Normal	87.1	29.6	61.1	75.3	79.6	105.7	132.3
Schizophrenic patients	90.1	39.2	63.6	73.1	78.8	101.3	118.8
Systolic blood pressure (mm. of mercury)							
Normal	119.7	124.6	117.1	111.1	110.9	130.7	130.7
Schizophrenic patients	109.2	114.8	108.9	107.1	103.5	115.6	115.5
Diastolic blood pressure (mm. of mercury)							
Normal	76.6	70.0	67.2	69.9	70.6	68.8	67.6
Schizophrenic patients	74.0	68.6	65.5	67.4	66.9	65.8	66.2
Pulse rate (beats per minute)							
Normal	72.0	83.8	69.5	66.5	65.3	72.1	76.6
Schizophrenic patients	69.2	72.8	73.5	69.7	69.1	76.3	77.8

used as control figures for the epinephrine tolerance test. These readings were similar for the two groups; so it may be considered that they started at the same base line. A half-hour after the injection of epinephrine the mean for the normal subjects had risen 26.1 mg., and in one hour 52.7 mg. per hundred cubic centimeters. The corresponding increases in blood sugar for the patients were 22.5 and 40.0 mg. per hundred cubic centimeters. The response to exogenous epinephrine was definitely less in the patients; this seems to corroborate the previous observation of a probable lessened reactivity to endogenous adrenal activity.

The results discussed heretofore have been limited only to trends and give little indication of the individual changes. These are shown

6. Cannon, W. B.: The Wisdom of the Body, New York, W. W. Norton & Company, Inc., 1932, p. 113.

in figure 1. Each level of the blood sugar at a given time in the procedure is represented by a black dot (for patients) or by an open circle (for normal subjects). The fasting levels show a similar distribution for the two groups of subjects, except in the case of 2 patients whose blood sugars were 119 and 127 mg. per hundred cubic centimeters. At the half-hour point, however, there is a distinct difference. The 20 normal subjects are grouped compactly between the levels of 19 and

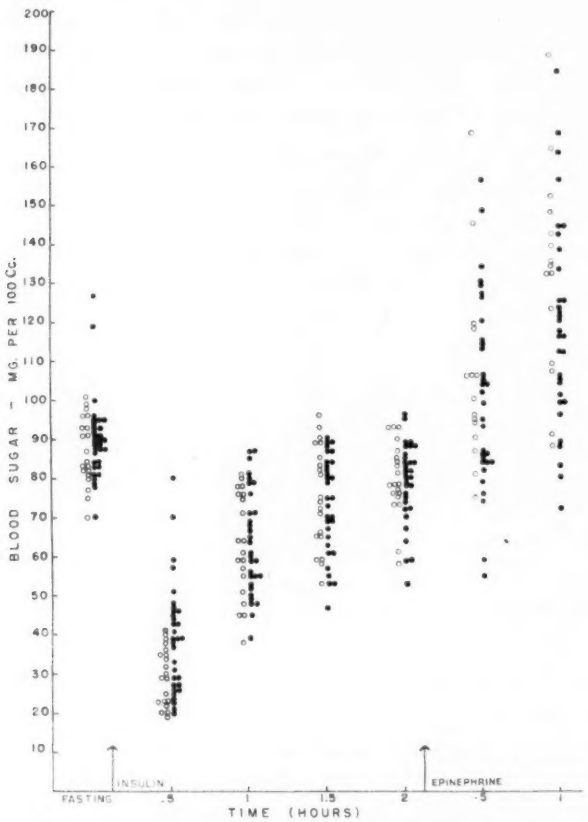

Fig. 1.—Frequency distributions of individual values for blood sugar obtained during the course of insulin and epinephrine tolerance tests on 32 male schizophrenic subjects (black dots) and 20 normal men (open circles).

41 mg. per hundred cubic centimeters. Within this range are found the values for 19 of the patients, or 59 per cent of the total number. The other 13 patients had blood sugar levels that were higher than any of the normal subjects, up to 80 mg. per hundred cubic centimeters. At the next reading, a half-hour later, the values for the normal subjects were again essentially at the same levels as those for the patients, which

indicates their seemingly more rapid recovery. During the next hour the values for the two groups continued to show a similarity of distribution. It should be noted that after the administration of insulin the range of values was slightly increased in comparison with the fasting levels, except at the thirty minute period in the case of the normal subjects. This means that in the hypoglycemic phase the normal subjects reacted to the acute effects of insulin much more homogeneously as a group than did the schizophrenic patients, but that in the stage of recovery the subjects in the two groups differed more widely from each other than during the control period.

After the administration of epinephrine the levels of blood sugar scatter widely, much more so than after the injection of insulin. This may be due to the fact that intramuscular injection affords many more possibilities for individual differentiation on account of the variation in blood supply than does the intravenous route. Another possibility may be that a downward trend of the blood sugar level is more limited, physiologically than an upward trend. The distributions for the two groups show great similarity to each other, however. It is only in the second half-hour that the normal subjects show a trend to higher levels than do the patients. This is primarily due to the fact that the blood sugar level for many of the patients remained the same, or even decreased, in the second half-hour after the injection of epinephrine. In the case of the normal subjects there were no decreases during this time. It would seem, then, that the normal subjects tended to have a more sustained effect in this regard than did the patients.

As has been seen, the response of the blood sugar to insulin can be divided into two phases: the initial decrease, which is an index to insulin sensitivity, and the secondary rise, which shows the responsiveness to hypoglycemia. Forty-one per cent of the patients showed greater resistiveness to insulin than did any of the normal subjects. The recovery phase would seem, also, to be more sluggish than normal, as indicated by values in table 1 and figure 1. The evidence in the literature on the latter point is conflicting. Horvath and Friedman [2] stated that schizophrenic patients are less reactive in this respect. Meduna, Gerty and Urse [3] found that serum from schizophrenic patients shows an insulin-inactivating effect over a longer period than does normal serum. We have endeavored to clarify this point by determining the relationship between the blood sugar levels at the thirty minute period, that of maximum hypoglycemia, and the changes in blood sugar in the next thirty minutes, at which time there is the greatest degree of recovery. The results are seen in the scatter diagram in figure 2. There is a negative correlation between the thirty minute values and the changes in the next half-hour, which indicates that the more intense the hypoglycemia the greater the rebound from it. For example, a

blood sugar, level of 20 mg. per hundred cubic centimeters will increase 40 mg. per hundred cubic centimeters in the next thirty minutes, while the corresponding change for a blood sugar reading of 60 mg. will be only 0 to 5 mg. per hundred cubic centimeters. Thus, the change is dependent on the hypoglycemic level. Since the schizophrenic patients, whose blood sugars lay within the normal range, showed the same increase as did the nonpsychotic subjects, it may be concluded that the recovery from hypoglycemia was adequate in the patients and that their apparent sluggishness was due solely to the fact that the blood sugar level of some of the psychotic subjects was not low enough to activate the blood sugar–raising mechanisms.

The cardiovascular reactions following the administration of insulin and epinephrine are shown in table 1. The characteristic changes with

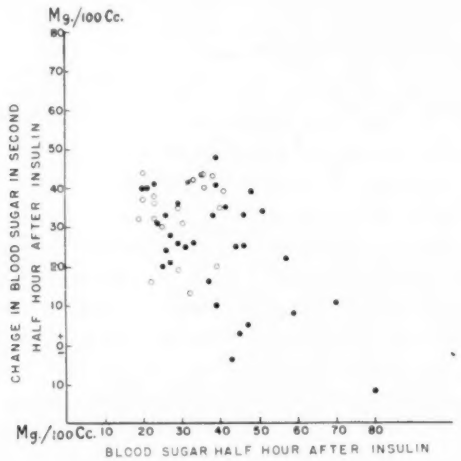

Fig. 2.—Scatter diagram illustrating the relationship between the blood sugar values obtained thirty minutes after the injection of insulin and the change from such levels in the subsequent thirty minutes, as observed in 32 male schizophrenic subjects (black dots) and 20 normal men (open circles).

insulin were an increase in systolic pressure, a decrease in diastolic pressure and an increase in pulse rate. The greatest changes were usually seen at the period of maximum hypoglycemia. Subsequently, there was a resumption to or below the control level, which may have been due to the prolonged rest in bed. Epinephrine resulted in a similar picture. There was a tendency to a greater degree of reactivity in the normal subjects. After insulin they showed an average increase in pulse rate of 12 beats per minute, as compared with 4 beats per minute for the patients. After injection of epinephrine their systolic blood pressure increased 20 mm. of mercury and their pulse rate 12 beats

per minute, as compared with a corresponding change of 12 mm. of mercury and 9 beats per minute for the psychotic group.

While this greater reactivity of the normal subjects in the blood pressure and the pulse rate parallels the greater changes in blood sugar, there is no relationship between the cardiovascular and glycemic variations within the individual subject. There may undoubtedly be a common factor, but it is not apparent on a simple basis. In addition, the reactions after insulin show no correlations with those after epinephrine in blood sugar content blood pressure or pulse rate, so that the role of the adrenomedullary secretion in the insulin reaction cannot be a dominant one.

The hypoglycemic reaction to insulin showed no relationship to age, duration of hospitalization or subtype of psychosis.

TABLE 2.—*Means of Values for Blood Sugar Obtained in the Course of Two Insulin and Epinephrine Tolerance Tests on Nine Schizophrenic Subjects, with Average Differences Between Readings Taken at Similar Times*

		After Insulin				After Epinephrine	
	Fasting	0.5 Hr.	1 Hr.	1.5 Hr.	2 Hr.	0.5 Hr.	1 Hr.
Mean values on first test..... (mg. per 100 cc.)	86.1	41.7	65.1	76.4	82.3	111.9	119.7
Mean values on second test..... (mg. per 100 cc.)	85.7	40.2	60.8	76.0	77.1	99.5	108.1
Average individual differences..... (mg. per 100 cc.)	7.8	4.8	10.4	15.9	7.7	24.6	22.9

The subjective reactions to insulin are of some interest. The characteristic symptoms during the hypoglycemic phase included a varying degree of fatigue and drowsiness, slight blurring of vision, sweating, tachycardia and hunger. No subject lapsed into unconsciousness despite the low levels of blood sugar. There was a good deal of individual variation in symptoms. When they were pronounced, the blood sugar was always low. However, in some subjects with low values after insulin few signs were evident. Thus, the relationship between the blood sugar level and these attendant phenomena was not great.

In order to evaluate the consistency of the figures obtained, insulin and epinephrine tolerance tests were repeated on 9 schizophrenic subjects with the same doses of the substances and under exactly similar conditions. These repetitions were made not later than one week after the first test in all but 1 case, in which the test was done after an interval of two months.

The average values for the two tests are shown in table 2. The means of the values for insulin tolerance were similar, particularly at the half-hour reading, which indicates, therefore, the reliability of

this figure. Two hours after the injection of insulin the figures for the second test were slightly lower than those for the first. After injection of epinephrine, however, there was a greater difference between the two readings. The values obtained in the first test were quite comparable to those for the larger group of patients. On repetition, however, the mean blood sugar levels were 11 mg. per hundred cubic centimeters lower. The reason for this lesser reaction is difficult to explain in view of the similarity of the previous portion of the curve. At any rate, the result does not invalidate the difference in values between the larger group of patients and the normal subjects, but strengthens it. Since the mean values show only the general trend, we have computed the variation between the two blood sugar values for each subject taken at identical points on the curve. For the insulin tolerance the average difference between the two readings was usually under 10 mg.[7] per hundred cubic centimeters. At the point of maximum reaction, it was no greater than 4.8 mg. per hundred cubic centimeters. Since this is less than the difference between the large group of patients and the normal group, it would seem that these results are reliable. This appears to be particularly true since the reactions of the normal subjects were much more homogeneous and on that basis would be expected to show less variation for the individual subject. One would assume, therefore, considerable consistency in this procedure.

The case is somewhat different with epinephrine. Not only did the subjects vary widely from each other in their reaction to this substance, as shown in figure 1, but there was a good deal of fluctuation in the reaction of each subject. The average variation lay between 20 to 25 mg. per hundred cubic centimeters, a figure which may cast some doubt on the reliability of the difference between normal and schizophrenic subjects. Whether this procedure is sufficiently consistent to be reliable is at present a question.

COMMENT

The results of the study indicate that a certain proportion of schizophrenic patients show less responsitivity to insulin than do normal subjects. Thus, from this point of view, the patients can be divided into two types, a differentiation which is not paralleled by variations in the psychiatric status. Our results are in agreement, therefore, with those of Meduna, Gerty and Urse.[3] They are not consistent with the conclusions of Gellhorn, Feldman and Allen,[4] who postulated a predominance of vagoinsulin influence in schizophrenic patients as compared with normal subjects, but demonstrable only in a state of excitement. Our

7. The value of 15.9 mg. per hundred cubic centimeters at the one and one-half hour point is due primarily to the variation in 1 patient of 53 mg. per hundred cubic centimeters.

results for the blood sugar, on the basis of the theory of an antonomic imbalance, suggest greater reactivity in the sympathicoadrenal sphere in the patients, since the hypoglycemic results of insulin were apparently antagonized. However, since this theory does not seem to coincide with the characteristic features of the schizophrenic state, some other explanation must be forthcoming. The specific factors responsible for the insulin sensitivity are probably of endocrine origin, since insulin resistance has been noted to be a feature of endocrinopathies involving the adrenal cortex, the thyroid and the pituitary gland.[1] It is of interest that hypometabolism [8] and an abnormal reactivity to a glycerin extract of adrenal cortex [9] have been characteristic of many cases of schizophrenia. The role played by the carbohydrate metabolism of the liver and tissues, independent of or associated with such hormonal factors, offers further problems.

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An investigation was made of the glycemic and autonomic reactions of 32 schizophrenic and 20 normal men. Forty-one per cent of the patients showed some degree of resistance to insulin. The reactions to hypoglycemia were the same in the two groups. A lessened reactivity in blood sugar following the injection of epinephrine was noted in the patients. In general, the normal subjects showed greater changes in the blood pressure and pulse rate, paralleling the differences in the blood sugar between the two groups.

Worcester State Hospital.

8. Hoskins, R. G., and Sleeper, F. H.: Organic Functions in Schizophrenia, Arch. Neurol. & Psychiat. **30**:123 (July) 1933.

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CEREBRAL DYSRHYTHMIA IN RELATION TO ECLAMPSIA

MILTON ROSENBAUM, M.D.
AND
GEORGE L. MALTBY, M.D.
CINCINNATI

The toxemias of pregnancy are usually classified as (1) preeclampsia (toxemia grade 1, or grade 2 in some clinics) and (2) eclampsia, this term being reserved for the condition in which convulsions or coma develops in the presence of the toxemia. The cause of these toxemias is not known. Most authorities believe that they are etiologically similar, and therefore a single disease entity.[1] However, why one patient has convulsions as part of the syndrome and another remains free of seizures is not clea- ... problem of the toxemias that this pap

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TABLE 1.—*Summary of Pertinent Data Related to the Diagnosis of Eclampsia in 20 Patients*

	Age, Year	Color	No. of Pregnancies	Pregnancy in Which Attack Occurred	Blood Pressure (High)	Urinary Albumin	Edema	Serologic Reaction
1	24	B	5	1st, 4th, 5th	200/130	+++	+	—
2	23	B	3	3d	190/100	++	+	—
3	24	B	3	3d	170/120	+	+	—
4	18	B	2	2d	180/100	++	+	—
5	22	B	5	5th	170/100	+	+	+
6	20	W	1	1st	140/ 90	++	+	—
7	15	B	1	1st	196/110	++	—	—
8	25	B	6	6th	210/130	++	+	—
9	17	B	1	1st	180/110	+	+	+
10	22	W	1	1st	176/110	+++	+	—
11	24	W	1	1st	160/ 95	++	—	—
12	18	B	3	3d	190/110	+++	+	—
13	19	B	2	1st	154/102	++	+	—
14	41	B	9	9th	212/134	++++	+	—
15	36	W	2	1st	160/100	+	+	—
16	18	W	1	1st	200/110	+++	+	—
17	19	W	1	1st	175/110	+	+	—
18	32	B	12	9th	190/140	—	—	—
19	32	B	3	3d	138/106	+++	+	—
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TABLE 2.—*Summary of Pertinent Data Related to the Diagnosis of Preeclampsia in 20 Patients*

	Age, Year	Color	No. of Pregnancies	Pregnancy in Which Attack Occurred	Blood Pressure (High)	Urinary Albumin	Edema	Serologic Reaction
1	24	B	2	2d	190/110	+	—	—
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8	27	W	4	4th	190/115	+	+	—
9	24	B	1	1st	164/100	++	+	—
10	38	W	6	6th	240/132	++	+	—
11	17	W	2	2d	158/115	++	—	—
12	30	B	5	5th	168/110	—	+	+
13	32	W	5	5th	154/ 90	—	+	—
14	43	W	12	12th	148/ 92	+	+	—
15	23	B	2	2d	150/102	—	—	+
16	16	B	1	1st	184/104	+	—	—
17	16	B	1	1st	160/110	+	—	—
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cent of the tracings of the eclamptic groups (15 patients) were taken from six months to five years after the attack, while in the preeclamptic group (10 patients) 50 per cent of the tracings were taken from one to two years after the attack. The intervals are adequate in most, if not in all, instances to exclude postconvulsive

this figure. Two hours after the injection of insulin the figures for the second test were slightly lower than those for the first. After injection of epinephrine, however, there was a greater difference between the two readings. The values obtained in the first test were quite comparable to those for the larger group of patients. On repetition, however, the mean blood sugar levels were 11 mg. per hundred cubic centimeters lower. The reason for this lesser reaction is difficult to explain in view of the similarity of the previous portion of the curve. At any rate, the result does not invalidate the difference in values between the larger group of patients and the normal subjects, but strengthens it. Since the mean values show only the general trend, we have computed the variation between the two blood sugar values for each subject taken at identical points on the curve. For the insulin tolerance the average difference between the two readings was usually under 10 mg.[7] per hundred cubic centimeters. At the point of maximum reaction, it was no greater than 4.8 mg. per hundred cubic centimeters. Since this is less than the difference between the large group of patients and the normal group, it would seem that these results are reliable. This appears to be particularly true since the reactions of the normal subjects were much more homogeneous and on that basis would be expected to show less variation for the individual subject. One would assume, therefore, considerable consistency in this procedure.

The case is somewhat different with epinephrine. Not only did the subjects vary widely from each other in their reaction to this substance, as shown in figure 1, but there was a good deal of fluctuation in the reaction of each subject. The average variation lay between 20 to 25 mg. per hundred cubic centimeters, a figure which may cast some doubt on the reliability of the difference between normal and schizophrenic subjects. Whether this procedure is sufficiently consistent to be reliable is at present a question.

COMMENT

The results of the study indicate that a certain proportion of schizophrenic patients show less responsitivity to insulin than do normal subjects. Thus, from this point of view, the patients can be divided into two types, a differentiation which is not paralleled by variations in the psychiatric status. Our results are in agreement, therefore, with those of Meduna, Gerty and Urse.[3] They are not consistent with the conclusions of Gellhorn, Feldman and Allen,[4] who postulated a predominance of vagoinsulin influence in schizophrenic patients as compared with normal subjects, but demonstrable only in a state of excitement. Our

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In recent years, with the aid of the electroencephalographic technic, a good deal of light has been shed on the problem of convulsive disorders. Many aspects of the clinical picture of the toxemic syndrome suggested the necessity of electroencephalographic studies. In a preliminary report we have briefly discussed our observations on a small series of eclamptic and preeclamptic patients.[2] This communication deals further with the electroencephalographic patterns and the family histories in a larger group of similar patients.

MATERIALS AND METHODS

Forty unselected patients, 20 of whom had eclampsia and 20 preeclampsia, were included in this study. With the exception of 4 patients (3 with eclampsia and 1 with preeclampsia), all had been admitted to the obstetric service of the Cincinnati General Hospital during the past five years. Each patient met the requirements recently given by Dieckman[1] for the diagnosis of eclampsia and preeclampsia. The symptoms, which included hypertension, edema, albuminuria and convulsions, are summarized in tables 1 and 2.

A thorough history was obtained on each patient by one of us emphasizing the following points: (1) history of previous convulsions, (2) history of convulsive disorders in the family (including eclampsia) and (3) history of convulsions following the toxemia.

From the Departments of Psychiatry, Neurosurgery and Neurology, University of Cincinnati College of Medicine and Cincinnati General Hospital.

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changes as a cause of the abnormal tracings. In this respect it is interesting that of the 10 tracings recorded for the preeclamptic patients within two weeks after delivery, only 2 revealed abnormalities. These observations were of aid in ruling out any obvious cerebral dysrhythmias which may have arisen from the pregnancy and parturition.

The electroencephalographic technic consisted of six lead monopolar recordings, with the lobe of the ear as a reference point. The leads were taken from the frontal, parietal and occipital regions. Short periods of hyperventilation were included in each record. From the scalp electrodes the potentials were led off to Grass amplifiers and recorded on a three channel ink writer. The records were analyzed according to the standards suggested by Gibbs and Gibbs,[3] Jasper and Kershman[4] and Davis,[5] and more recently by Williams,[6] which include criteria for frequency, amplitude, wave form and general stability. The tracings were interpreted by one of us (G. M.) without knowledge of the patient's obstetric diagnosis and history.

TABLE 3.—*Time Interval Between Delivery and Recording of the Electroencephalogram in the Eclamptic and the Preeclamptic Group*

Time After Delivery in Which Electroencephalogram Was Recorded	Number of Patients			
	Eclampsia		Preeclampsia	
	Number	Percentage	Number	Percentage
1 wk.	2	10	6	30
2 wk.	3	15	4	20
6 mo.	1	5	0	..
1 yr.	6	30	4	20
2 yr.	5	25	6	30
3 yr.	1	5	0	..
5 yr.	2	10	0	..
Total	20	100	20	100

RESULTS

The results of this study are graphically depicted in figures 1 and 2. Thirteen (65 per cent) of the 20 patients with eclampsia had abnormalities (cerebral dysrhythmias) in their electroencephalograms, while only 2 (10 per cent) of the patients with preeclampsia had similar abnormalities (fig. 1). The abnormalities encountered (figs. 3 and 4) were for the most part similar to those seen with the convulsive disorders (epilepsy) in that they revealed dysrhythmias characterized by slow waves with increased voltage.

3. Gibbs, F. A.: Interpretation of the Electroencephalogram, J. Psychol. **4**:365, 1937. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941.

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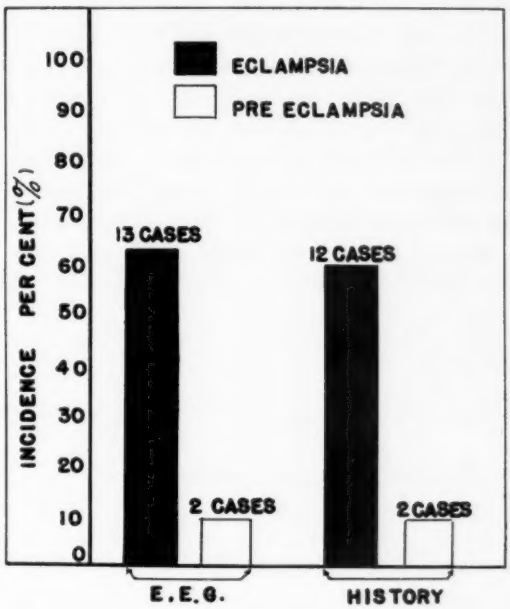

Fig. 1.—Incidence of abnormal electroencephalograms and of family histories of convulsive disorders in 20 eclamptic and 20 preeclamptic patients.

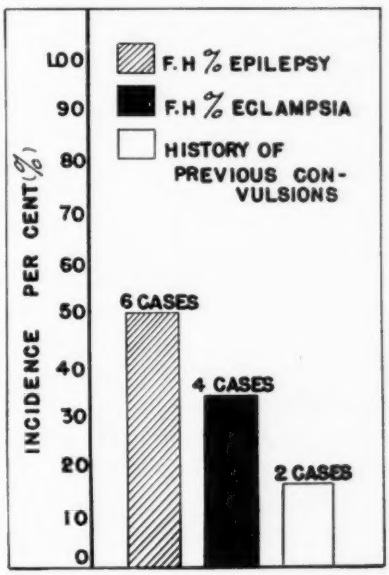

Fig. 2.—Analysis of 12 cases of eclampsia with a history of convulsive disorders. In 6 cases there was a family history of epilepsy, in 4 cases a family history of eclampsia and in 2 cases a history of previous convulsive episodes in the patient.

The historical data revealed that a convulsive diathesis existed in 12 (60 per cent) of the eclamptic patients, as contrasted with 2 (10 per cent) of the preeclamptic patients fig. 1). The data on the eclamptic group have been analyzed in figure 2. Six of the patients gave a history of epilepsy in one or more members of the immediate family. In 4 additional patients the history of convulsions was limited to an attack of eclampsia in one member of the immediate family. In 1 of these 4 patients eclampsia developed in the first pregnancy, and since then she has had frequent grand mal attacks (epilepsy) and is responding well to dilantin therapy. The remaining 2 patients gave a history of

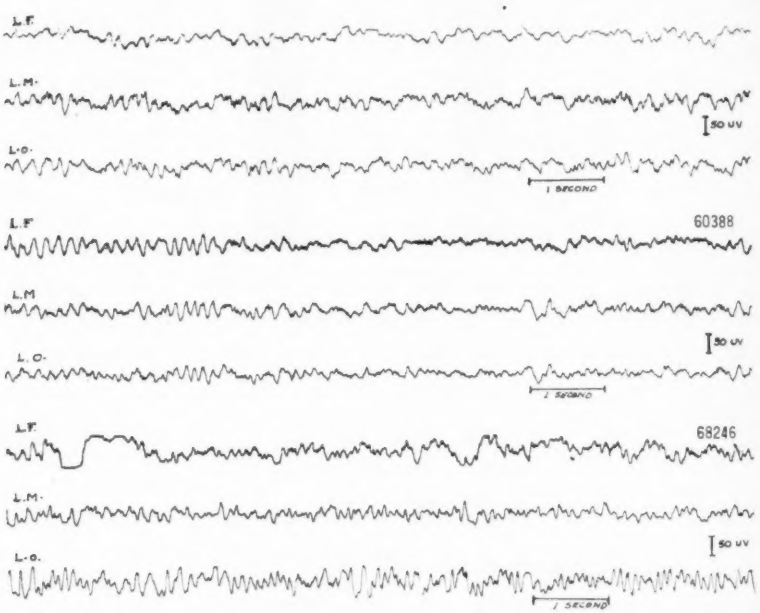

Fig. 3.—The electroencephalographic tracings for 3 eclamptic patients recorded from the left frontal, motor and occipital areas. These recordings were made during the resting stage. Note the obvious scattered slow waves, many of high voltage, and the general appearance of instability in all three records.

convulsive episodes previous to the attack of eclampsia. One of these patients had an interesting history in that as a child she suffered from petit mal episodes and in adolesence there was an occasional grand mal attack. In her first pregnancy toxemia developed, and during the eighth month she went into severe "status epilepticus." After recovery the patient had more frequent grand mal attacks, which recently have been controlled by dilantin therapy.

A few comments regarding the data in tables 1 and 2 may be of interest. Of the 20 eclamptic patients, 14 were Negroes and 6 were white

persons, while 11 of the preeclamptic patients were Negroes and 9 were white persons. These figures probably reflect the incidence of white persons and Negroes in the obstetric service. The average age of the eclamptic patients was 24 years, as compared with a corresponding age of 29 years for the preeclamptic patients. Ten (50 per cent) of

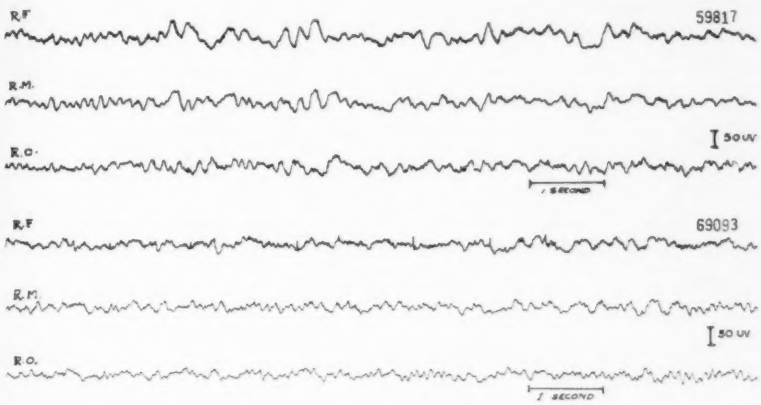

Fig. 4.—Electroencephalographic tracings for the 2 eclamptic patients with a history of previous convulsions. The recording was done during the resting stage. Note the prominent abnormalities, consisting of diffuse, high voltage, slow waves.

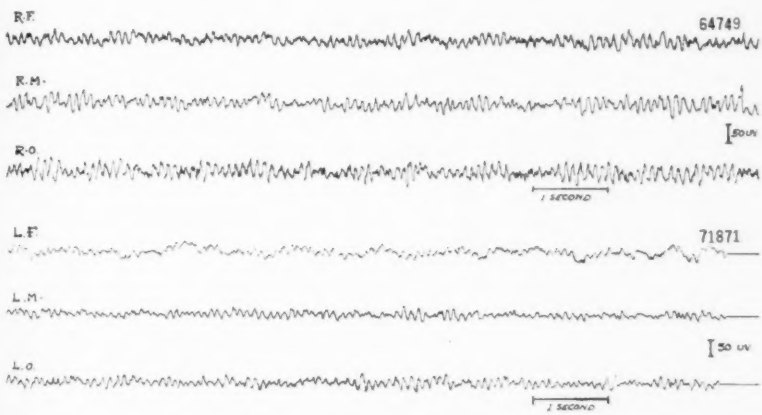

Fig. 5.—Normal electroencephalograms of 2 preeclamptic patients, showing a stable, 10 per second rhythm of normal voltage.

the eclamptic patients had the attacks in the first pregnancy, while only 5 (20 per cent) of the preeclamptic patients were stricken in the first pregnancy. Also, there were 7 primiparas with eclampsia as compared with 4 with preeclampsia. The foregoing data regarding the age incidence and the increased proportion of primiparas with eclampsia is in agreement with the observations of other authors.[1]

COMMENT

In recent years it has been demonstrated that patients suffering from convulsive disorders in the form both of "idiopathic" and of "symptomatic" epilepsy have more or less characteristic types of abnormalities in their electroencephalograms. Lennox coined the term "cerebral dysrhythmia" to indicate such abnormalities.[7] The excellent studies of Lennox, Gibbs and Gibbs[8]; Robinson[9] and Löwenbach[10] revealed that the cerebral dysrhythmia is an inherited characteristic, and it is this factor which predisposes one to the convulsive disorders. Although only 0.5 per cent of the general population suffers from clinical "epilepsy," it has been estimated in preliminary sampling by Lennox, Gibbs and Gibbs[11] that approximately 10 per cent of normal persons exhibit abnormalities similar to those seen in patients with seizures or related conditions. These persons with "asymptomatic dysrhythmia" may, of course, go through life without manifesting convulsive phenomena. On the other hand, in the face of conditions which affect the central nervous system, either by structural changes, such as brain tumor, trauma, encephalitis or syphilis, or by metabolic or physiopathologic, changes due to drugs, toxins, changes in the chemical constituents of the blood, etc., a predisposed person is more likely to have convulsions.[7]

Rosenbaum, Lewis, Piker and Goldman[12] noted that convulsions developed in 9 per cent of a large series of patients with delirium tremens, and they concluded that one of the basic etiologic factors responsible for the convulsion was the underlying predisposition in the form of an inherent cerebral dysrhythmia. Recently Foster[13] studied the association between convulsive seizures and rheumatic heart disease. He noted that the familial incidence of convulsive seizures or migraine appears in cases of rheumatic heart disease associated with seizures six times as frequently as in cases of rheumatic heart disease without seizures.

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The high incidence (65 per cent) of cerebral dysrhythmias, together with the high incidence (60 per cent) of a positive family history of convulsive disorders, found in this group of 20 eclamptic patients is striking. These results strongly suggest that there may be a primary cerebral dysrhythmia present in patients with the syndrome of eclampsia, and that the associated toxemia may be the "trigger mechanism" that exaggerates the inherent dysrhythmia to the degree that convulsions appear. These factors may help to explain the well known fact that eclampsia is more common in young primiparas. Signs of cerebral involvement have been noted pathologically, and of course clinically. Minute hemorrhages are frequent; edema and congestion are common, and occasionally gross cerebral hemorrhages have been observed in patients dying of toxemia. The convulsions have been considered to be dependent on the cerebral anoxemia resulting from cerebral vasoconstriction and/or edema.[1] These histopathologic and physiopathologic changes would thus constitute the cerebral "insult," or "trigger mechanism."

There is a paucity of material in the literature concerning the family history of convulsive disorders in cases of eclampsia. Apparently, most authors have limited the historical data to the question of a family history of eclampsia alone. Various citations have been made regarding isolated cases in which there was a family history of eclampsia. In the present study 4 of the eclamptic patients had such a history. However, the more detailed historical data gathered for this series point to a rather high incidence of convulsions (60 per cent) in the eclamptic group and further emphasize the important role of a "constitutional" predisposition to convulsions in patients with eclampsia.

Patients with epilepsy do not as a rule have more seizures during pregnancy.[14] However, if toxemia develops in a patient with epilepsy, it may be a different story. The case cited previously is pertinent. In childhood there had been petit mal attacks, and an occasional grand mal attack had occurred during adolescence. In the eighth month of the patient's first pregnancy toxemia and "status epilepticus" developed. Patients have had "idiopathic epilepsy" after an attack of eclampsia, and this course was experienced by 1 of the eclamptic patients considered previously in this study. Dexter and Weiss [15] reported the case of a patient with a negative personal history for epilepsy in whom grand mal seizures developed after eclampsia. A similar case was noted by DeLee.[16] It might be argued that such patients should not

14. Lennox, W. G., cited by Dexter and Weiss.[15]

15. Dexter, L., and Weiss, S.: Pre-Eclamptic and Eclamptic Toxemia of Pregnancy, Boston, Little, Brown & Company, 1941.

16. DeLee, J. B.: The Principles and Practice of Obstetrics, ed. 7, Philadelphia, W. B. Saunders Company, 1938.

be considered as having true eclampsia, but rather as having "epileptic convulsions associated with toxemia." In our opinion the underlying factor partially responsible for the convulsion—the inherent cerebral dysrhythmia—is the same in both instances, and whether or not the patient had had clinical convulsions previous to the toxemia is of little importance.

Dieckman [1] has presented statistical data on the incidence of the various types of toxemia in 1,100 toxemic patients. If consideration is limited only to those toxemias peculiar to pregnancy (preeclampsia and eclampsia), it may be noted that 47 per cent of the patients had preeclampsia and 4.4 per cent eclampsia. Thus, 10 per cent of the patients with true toxemia of pregnancy had convulsions (eclampsia). These figures are suggestive in view of the data presented by Lennox, Gibbs and Gibbs [11] to the effect that about 10 per cent of the normal population is predisposed to convulsive disorders.

This study strongly suggests that a person who is predisposed to convulsions, as evidenced by an inherent cerebral dysrhythmia or a family or personal history of convulsive disorders, is likely to exhibit convulsions in the presence of toxemia of pregnancy. In the past this syndrome has been termed eclampsia.[17] These studies are not concerned in any regard with the cause of the toxemia. In accord with this concept is the fact that many of the methods that have been successful in the therapy of eclampsia have depended on the use of anticonvulsant drugs (magnesium sulfate, sedatives, etc.).

It may be inferred that a careful history, together with an electroencephalogram, may be of great importance in determining in whom eclampsia may develop. Furthermore, it is apparent that the proper prophylactic therapy of such persons might include measures generally employed in the treatment of cerebral dysrhythmias (anticonvulsant drugs).

SUMMARY AND CONCLUSIONS

Thirteen, or 65 per cent, of 20 patients with eclampsia had electroencephalograms indicative of cerebral dysrhythmia, as compared with 2, or 10 per cent, of 20 patients with preeclampsia.

17. Since the term "eclampsia" refers to the toxemia of pregnancy associated with convulsions, it would seem that "preeclampsia" should refer to the same condition before convulsions appear. Thus, "preeclampsia" implies that convulsive phenomena are possible. However, our conclusions would make the term "preeclampsia" illogical. The absence of convulsions in "nonconvulsive toxemia of pregnancy" is due not to the fact that for some reason the possible convulsion has not appeared, but to the patient's innately stable cerebral rhythm. Therefore, some term other than "preeclampsia" should be used to designate "nonconvulsive toxemia of pregnancy."

Twelve, or 60 per cent, of patients with eclampsia had a family and personal history of convulsive disorders, while only 2, or 10 per cent, of the preeclamptic patients had a similar history.

It is suggested that a primary cerebral dysrhythmia may be present in those patients having the syndrome of eclampsia, and that the associated toxemia may be the "trigger mechanism" that exaggerates the inherent dysrhythmia to the degree that convulsions appear.

A careful history, together with an electroencephalogram, might be of aid in predicting in whom eclampsia may develop.

The prophylactic therapy of eclampsia may include the use of anticonvulsant drugs.

Dr. Richard Bryant and the other members of the obstetric staff cooperated in this study.

Technical assistance was given by Mrs. Edward V. Brookfield.

INTRACRANIAL EPIDERMOIDS OCCURRING SIMULTANEOUSLY BELOW AND ABOVE THE TENTORIUM

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The term epidermoid (cholesteatoma) refers to a slow growing, cystic neoplasm which may occur in or beneath the scalp, within or about the orbit, in the neck, jaws, middle ear, mastoid, cranial bones or elsewhere along the craniospinal axis. The manner of origin is said to be by inclusion of epiblastic tissue during the closure of clefts or at a point of contact of ectodermal invagination with other tissues in the development of the embryo.[1] Another presumptive source is epidermal implantation resulting from trauma, an example of which has been recorded by Graumann.[2] Up to the time of writing 205 cases of intracranial epidermoid tumor have been recorded in the literature. Of this number there were 7 in which the lesion was situated in both the supratentorial and the infratentorial position. The purpose of this paper is to review these 7 cases and to add the eighth. The following are brief abstracts of the cases given chronologically as they appeared in the literature.

PREVIOUS CASES

CASE 1 (reported by Price,[3] 1887).—L. F., a widow aged 39, was attended in the outpatient department of the Berkshire Hospital during December 1886 and January 1887. The initial symptoms were not given, but the illness was of five years' duration and was characterized as steadily progressive. One year after onset vision was lost in the right eye. Later there were attacks consisting of a sudden, queer feeling in the head, falling, dropping of articles from the hand and urinary incontinence. Examination disclosed that the right optic nerve head was white, the left one pale and the vessels of the fundi thin. Gradually the patient lost ground, suffered from recurrent convulsive seizures and died on Jan. 28, 1887.

Autopsy revealed a tumor of the brain and several areas of caseous tuberculosis in the apex of the left lung. Before the Pathological Society of London on March 3, 1887 Price presented the brain, over the base of which a large,

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From the Neurological Unit of The Brooklyn Hospital.

1. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 1051.

2. Graumann, G.: Ueber ein traumatisch entstandenes Cholesteatom der hinteren Schadelgrube, Zentralbl. f. Chir. **64**:1154-1161 (May 15) 1937.

3. Price, J. A. P.: Cholesteatoma at the Base of the Brain, Tr. Path. Soc. London **38**:24-26, 1887.

irregularly nodular, brittle tumor spread from the medulla oblongata to the optic chiasm, displacing the temporal lobes laterally. On the medulla was a smaller tumor of the same characteristics, which contained sebaceous-like material. The growth appeared encapsulated by a thin membrane which was continuous with the pia-arachnoid and had a mother-of-pearl sheen. Aside from the areas of compression the brain appeared normal. On microscopic examination numerous cholesterol crystals and the outlines of several cells devoid of nuclei were seen.

Case 2 (reported by Frank,[4] 1889).—A man aged 43 was admitted to an asylum for the insane at the age of 39 (1879) because of peculiar and incessant talking. On examination he was found to have left hemiparesis, prominent eyes and strabismus on the right. In May 1881 a convulsion took place, and in February 1883, paresis of the extremities of the right side developed after another convulsion. A few months later the right upper extremity alone was involved in violent, jerking movements, after which the paresis of the extremities of the right side increased. More seizures ensued, implicating sometimes the right and at other times the left side. Death occurred during a particularly severe convulsion in January 1884.

Postmortem examination revealed a transparent, glossy growth the size of a chicken's egg in the region of the right operculum, which destroyed this structure and extended in the form of numerous pea-sized masses to envelop the optic chiasm and the right optic tract. A more spongelike and transparent portion of the tumor was directed posteriorly, where it covered the cerebral peduncles and the pons. At the pontobulbar junction was another neoplasm (apparently not connected with the first) measuring 3 by 2.5 by 1 cm. Histologically the two masses were alike, showing webbing of epithelial cells and cholesterol crystals.

Case 3 (reported by Nehrkorn,[5] 1897).—A man aged 44 was admitted to the hospital on June 15, 1894. About 1894 he had become depressed and complained of loss of appetite and sleeplessness. During the weeks just before admission he had been restless and mentally disturbed. Examination revealed that the left pupil was larger than the right and the facial muscles were flaccid, particularly on the left side. A fissure at the left corner of the mouth and excoriations of the scalp were ascribed to syphilis. The psychologic aberrations became rapidly greater, necessitating forced feeding, and after a period of coma the patient died July 28, 1894, supposedly of dementia paralytica.

Autopsy revealed complete absence of the left frontalis and masseter muscles. In the left cerebellopontile angle was a white, crumbly mass consisting of mother-of-pearl, glossy particles of skin, in which were embedded the sixth through the tenth cranial nerves of this side. The pons and medulla were compressed and displaced to the right by the tumor. Situated in the left temporo-occipital region of the cerebrum was another and larger tumor about the size of an apple, almost covered by cerebral tissue and partly encapsulated. The temporal horn of the left lateral ventricle was partly occupied by the neoplasm, although the ependyma remained intact. A white membrane of arachnoid webbing covered the base of the growth. Microscopic examination showed keratinized, desquamated epithelium but no hair or sudorific glands. (No description of the capsule was given.)

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4. Frank, C.: Ueber einen in der Dürener Irrenanstaltbeobachteten Fall von Cholesteatom, Allg. Ztschr. f. Psychiat. **46**:30-38, 1889.

5. Nehrkorn, A.: Ein Fall von meningealer Perlgeschwulst, Beitr. z. path. Anat. u. z. allg. Path. **21**:73-103, 1897.

Case 4 (reported by Strauss,[6] 1913).—A woman aged 32 was admitted to Mount Sinai Hospital on Oct. 5, 1909, complaining of pains in the joints, difficulty in chewing and swallowing and earache. She was the mother of three children, the youngest being 16 months old. The onset of her illness began in 1906 with disturbance of menstruation, the periods occurring every two to three months. At about this time there was an increase in weight, and headache developed. Eleven months prior to admission signs of mental derangement became evident. The headaches became more frequent and severe and were associated with nonprojectile vomiting. There was almost continuous gnashing of the teeth; the eyesight failed, and there were loss of memory for recent events, increased gain in weight, abnormal thirst and absence of menstrual flow during the last four months. Examination disclosed mental blunting. The facies were suggestive of acromegaly; the axillary and the pubic hair was sparse, and the subcutaneous fat was unusually sensitive. The optic fundi were normal. Glycosuria was present. On April 10, 1910 the patient was transferred to Montefiore Hospital. At this time the right optic nerve head was white and the left pale, and there was apparent bitemporal hemianopia. Stupor developed and terminated in death on Dec. 21, 1911.

Postmortem examination was confined to the head. On the under side of the brain a cystic, gelatinous mass extended from the inferior level of the olivary bodies to the optic chiasm. The pons was partially compressed by the largest prominence of the mass, while the region of the left basal ganglia was occupied by another large portion of the tumor, a projection of which extended into the cavity of the left lateral ventricle and another into the left frontal lobe. The neoplasm measured 4 cm. transversely and 5 cm. anteroposteriorly. The pathologic diagnosis was "cholesteatoma."

Case 5 (reported by Bailey,[7] 1924).—B. A., a man aged 40, was admitted to the Peter Bent Brigham Hospital on Nov. 14, 1922, complaining of loss of eyesight. In 1917 headaches prompted the patient to consult an oculist, who found that the visual acuity of the left eye was much reduced. By 1919 visual impairment had progressed to the point where he was no longer able to fulfil his duties as a salesman. During the year prior to admission there was physical weakness with loss of libido. Examination disclosed bilateral "primary" optic nerve atrophy, and vision in the right eye was restricted to perception of large objects in the lower left field. No other abnormal neurologic signs were demonstrable. On Nov. 27, 1922 a left transfrontal craniotomy was performed by Dr. Harvey Cushing. Between the optic nerves the rounded, glistening membrane of a pearly tumor, about 1 cm. in diameter, was visualized. After this portion was scooped out with a pituitary spoon, a mass the size of a golf ball was observed in the left middle fossa. This, in turn, was scooped out. It was then seen that the growth extended beyond the tentorium, and the operator followed this prolongation at least 5 cm. beyond the incisura. The cavity created by the removal of the tumor was filled with saline solution and the wound closed, no bleeding having been encountered. After a stormy course characterized by fever, fulness of the operative area and signs of meningeal inflammation, the patient improved, and he was discharged on Jan. 8, 1923. When interviewed in March 1923, he was in excel-

6. Strauss, I.: A Case of Cholesteatoma of the Brain, J. Nerv. & Ment. Dis. **40**:257-259, 1913.

7. Bailey, P.: Further Observations on Pearly Tumors, Arch. Surg. **8**:524-534 (Jan.) 1924.

lent physical condition but manifested mild psychologic disturbances. Pathologic examination of the material removed at operation disclosed a structure compatible with a diagnosis of epidermoid.

CASE 6 (reported by Cushing,[8] 1932).—A neurasthenic woman aged 43 was observed in the medical wards of the Peter Bent Brigham Hospital in 1926 for mitral stenosis, aortic insufficiency and severe headache. Partial deafness and other signs pointing to a neoplasm of the left cerebellopontile angle were noted at that time. In 1924 transient double vision had occurred, and the following year gradually increasing numbness of the left side of the face and attacks of dizziness and staggering were added to the symptoms. Later, pains in the distribution of the second and third divisions of the left trigeminal nerve were the presenting complaints and led to a second admission to the hospital on May 26, 1927—this time to the surgical service. The left eye protruded and deviated inward. The left side of the face was numb, but the deafness that had been noted during the previous admission had largely disappeared. "Fairly definite right-sided pyramidal symptoms were present." She was nervous and difficult to manage, and at her own request she was discharged without operation. During 1928 the symptoms grew worse, and periods of unconsciousness began to follow the headaches. On Dec. 6, 1928 the patient was admitted to the hospital for the third time, when, in addition to the previously described clinical picture, she presented neurokeratitis of the left eye. Because it was the impression that the trouble was a meningioma of the left gasserian ganglion sheath a craniotomy was undertaken. When the region of Meckel's cavity was exposed, the remnants of the ganglion were seen stretched over the glistening surface of a cholesteatoma, about 2 cm. in diameter. The tumor was thoroughly cleaned out and supposedly entirely removed, together with its enveloping membrane. Recovery was uneventful, and the patient was discharged on Jan. 23, 1929. The immediate result of the operation was alleviation of the pain formerly present in the distribution of the trigeminal nerve, but suspicion of an infratentorial extension of the original tumor was aroused when the "cerebellar" symptoms became more pronounced (the gait was ataxic; nystagmus was present, and there was symptomatic implication of all the cranial nerves on the left side, from the sixth through the twelfth). The patient was admitted to the hospital a fourth time, and on Nov. 8, 1929 operation disclosed a large cholesteatoma in the left cerebellopontile angle. The mass, together with its capsule, was removed, but in pursuing the membrane through the incisura tentorii the operator had to leave a fragment lying against the left cerebral peduncle. Recovery was prompt, but tinnitus became a presenting complaint, from which the patient subsequently had some relief by the use of drugs.

CASE 7 (reported by Alpers,[9] 1939).—K. M., a female, entered the hospital on March 30, 1936. Three years previously "Bell's palsy" had developed on the left side and persisted. This was followed two years later by staggering, which progressively increased, and three months before admission double vision developed. There had been no headache or vomiting. Examination gave evidence of impairment of the functions of the third and the fifth through the tenth cranial

8. Cushing, H.: Intracranial Tumors: Notes upon a Series of Two Thousand Verified Cases with Surgical Mortality Percentages Pertaining Thereto, Springfield, Ill., Charles C Thomas, Publisher, 1932, pp. 99-102.

9. Alpers, B. J.: Cerebral Epidermoids (Cholesteatomas), Am. J. Surg. **43:** 55-65 (Jan.) 1939.

nerves on the left side, weakness of the right hand and "hyperactive reflexes." Operation on April 2 exposed a large tumor which extended from the upper end of the spinal cord along the brain stem on the left through the incisura tentorii and disappeared beneath the temporal lobe. All of the mass within the posterior fossa and part of that in the middle fossa was removed. Convalescence was uneventful. Microscopic examination identified the growth as an epidermoid. There was no capsule, but the presence of many polyhedral cells together with the typical gross appearance of a pearly tumor led to the diagnosis of "cholesteatoma."

There are also reports in the literature which describe minor encroachments on the supratentorial or the infratentorial compartment, as the case may be, by a tumor situated predominantly on the other side of the tentorium, as in the case recorded by Rosenstein.[10] Here a huge epidermoid of the anterior and middle fossa sent sliver-like projections along either side of the pons for a short distance. However, such occurrences are not comparable to the cited cases and hence are not included in this group.

From the foregoing reports it is apparent that in 6 out of 7 instances there was nothing in either the history or the physical findings to excite suspicion concerning the true extent of the lesion. Although in the case reported by Cushing one might be led in retrospect to predict the existence of a mass situated in both the supratentorial and the infratentorial region, the difficulties encountered in arriving at the proper approach to the lesion by one so experienced in such matters indicates the pitfalls that may await others.

The following case seems to merit recording in detail since this experience indicates the difficulties encountered in establishing a diagnosis regarding the extent of the lesion even though ventriculographic studies were utilized.

REPORT OF A CASE

S. R., a 55 year old woman, was admitted to the neurologic unit of the Brooklyn Hospital under the care of Dr. Jefferson Browder on March 7, 1938. The patient complained of diminution of vision, impaired hearing in the right ear, tremors, clumsiness of the right hand and staggering gait.

The onset of the present illness was in 1930 (eight years prior to admission), when, without premonitory symptoms, a generalized convulsive seizure occurred during sleep. It was estimated that approximately fifty such attacks had taken place subsequently. At the outset the seizures came every second or third night; later, less frequently. No aura of any type had been experienced, and no resultant transitory paralysis had been observed by the family. For the next six years she was capable of carrying on her household duties and had no particular complaints except for the transient feeling of exhaustion for a day or so after each convulsive seizure. In the early part of 1937 vision was noted to be impaired—glasses had been worn for several years—consequently the eyes were reexamined

10. Rosenstein, A.: Pial Epidermoid of the Chiasmal Region, J. Mt. Sinai Hosp. **3**:216-223 (Jan.-Feb.) 1936.

and new lenses prescribed. This failed to correct the visual disturbance. In August 1937 the family of the patient noticed an unsteadiness in her gait without tendency to fall in any particular direction. This difficulty in walking grew slowly worse. In October 1937 there was a decrease in the acuteness of hearing in the right ear. About this time clumsiness of both hands developed, more pronounced on the right than on the left. Inability to perform skilled acts with the right hand resulted in a change from "right handedness" to "left handedness." At no time had there been any headache, vomiting or double vision. This history was obtained from the husband and the sister. The patient's statements were unreliable because of an obvious memory defect.

The patient was well developed and moderately obese; she was alert, responsive and not acutely ill. The optic fundi appeared normal save for absence of the physiologic cup of the right nerve head. The plotted visual fields showed an incomplete homonymous defect of the upper left fields. A Horner syndrome was present on the left, and lateral gaze of the left eye was limited. There was no weakness of the extremities, but gross ataxia of all extremities was evident, especially of the right lower limb. The deep reflexes were very active, more so on the right than on the left; the abdominal reflexes were not elicited. The response to plantar stimulation was normal on the left side and equivocal on the right. No abnormality of somatic sensibilities was demonstrated. In walking there was swaying to either side, and the right lower extremity was swung with a circumduction movement. In turning quickly to the right there was swaying. Romberg's sign was demonstrable, and even with the eyes open the position could not be maintained. On March 9, 1938 ventriculographic examination was performed. Fifty-five cubic centimeters of fluid was removed and replaced with air. The roentgenograms taken immediately after the injection of air presented a filling defect in the posterior part of the right lateral ventricle—indication of a mass situated lateral to the region of the right thalamus. No air was visualized in the aqueduct of Sylvius or the fourth ventricle. At operation, performed by Dr. Browder, the right lateral ventricle was opened near the atrium, and on the inferior surface of the ventricle was observed a smooth, whitish membrane covering a domelike projection into the cavity of the ventricle. The mass displaced the temporal portion of the choroid plexus, as well as the glomus, anteromedially. It appeared that the ependyma was absent from over the dome of the mass, although the termination of the contiguous ependyma could not be identified grossly. The membrane was sufficiently transparent for visualization of a whitish, fragmented material beneath it. After the presenting portion of the membrane was excised, the contents of the oval cavity, measuring approximately 6 by 4 by 3 cm., were removed. This material was crumbly and about the consistency of cottage cheese. The interior of the hollow was smooth and somewhat glistening; the surrounding structures did not tend to obliterate it immediately. No diverticulum or other alteration in the continuity of the interior of the sac was present. It was thought inadvisable to attempt complete removal of the capsule. Recovery from the operation was rapid. On the fifth day after operation it was observed by gross test that left homonymous hemianopia was present. Perimetric examination performed twenty-one days after operation showed slight narrowing of the left homonymous fields. The gait improved, but the visual deficit remained about the same. The patient was discharged from the hospital on March 30, 1938. Microscopic examination of the tissue removed at operation showed the membrane was a cyst wall lined by squamous epithelium; the white, cheesy material was composed of desquamated, keratinized epithelium and cholesterol crystals. During the ensuing year several generalized convulsions occurred. For six months there was improvement in

walking; however, from January to June 1939 increasing impairment of gait was observed.

The patient was readmitted to the hospital on June 20, 1939, complaining of increasing impairment of vision and difficulty in walking. Vision had become so poor that faces could not be recognized a short distance away. Memory defects, especially for recent events, had been noted by both the patient and her relatives and had become so pronounced that at times a sentence was left incompleted, the remainder of the thought lost. The unsteadiness of gait was more pronounced than prior to operation, in 1938, and was described as loss of "sense of balance." There had been four generalized convulsions, all occurring during sleep and observed by the relatives only after they were in progress. The left hand was used for skilled acts, owing to clumsiness of the right hand. There had been no nausea, vomiting, double vision or headache. On examination the patient was alert, rational, oriented and aware of her mental blunting. Conversation was well sustained, but memory was poor in all respects, and simple arithmetical calculations were performed incorrectly. There was obvious euphoria. The site of the previous right parietal bone flap was well healed; the area of decompression was soft, flat and pulsating. There was a Horner syndrome on the left side. Both pupils reacted sluggishly to light; the optic nerve heads were pale, and the retinal veins of the left eye were somewhat full. There were pronounced dyspraxia and ataxia of the extremities bilaterally. By mensuration the right grip was slightly weaker than the left. There was no notable alteration in deep reflexes. Of the abdominal reflexes, only that of the left lower quadrant could be obtained. The response to plantar stimulation was equivocal bilaterally. Standing without support was impossible. On June 23, 1939 ventriculographic examination was performed. Seventy cubic centimeters of fluid was removed and replaced with air. Roentgenograms disclosed symmetric dilatation of the lateral and third ventricles and an air-filled space on the right side corresponding to the site of the cyst evacuated at the previous operation. Neither the aqueduct of Sylvius nor the fourth ventricle was visualized. On June 28, 1939 suboccipital exploration was carried out by Dr. Browder. The cerebellar hemispheres were unduly prominent, the right being slightly more so than the left. The cerebellopontile angles were easily visualized, and nothing abnormal was disclosed. An incision was made in the mesial aspect of the right cerebellar hemisphere. At a depth of approximately 1 cm. a thin membrane was encountered, and when this was opened, it was obvious that the lesion here was similar to that previously encountered in the supratentorial region. After removal of the contents of the mass ample room was afforded the operator for careful inspection of the cyst wall. The cavity extended rostrally to a point estimated to be at the level of the incisura tentorii, and no diverticulum or other change in the wall suggested a site of possible supratentorial connection. The mesial wall of the cyst lay directly adjacent to the thinned-out dorsolateral wall of the fourth ventricle, but at no point was there gross defect in the ependymal lining. A portion of the wall of the fourth ventricle and of the adjacent capsule of the tumor was removed in order to establish direct communication of the cavity with the fourth ventricle. The wound was closed with layer silk. Recovery from the operation was prompt and without complication. By the time of discharge, July 19, 1939, vision had improved somewhat, and the Horner syndrome had cleared. There were moderate dyspraxia and ataxia of all extremities, more pronounced on the left than on the right, and walking was accomplished with but slight assistance. Position sense was moderately defective in all extremities. Microscopic examination of the specimen removed at the second operation disclosed material similar to that observed at the first operation.

At the last observation (July 1941) the patient was able to get about without assistance in her house, although she still required slight help when walking in the street; the intellect was improved, and the euphoric state was no longer evident. The optic nerve heads showed a mild degree of pallor. Although some decomposition of purposeful movements persisted, the dyspraxia had improved considerably, particularly in the right upper extremity, which now is being used for eating and knitting. No gross sensory changes were demonstrable. Recovery has not been as complete as had been anticipated. However, the patient is capable of carrying on her household duties.

COMMENT

The first report of a case of intracranial epidermoid is cited as being published by Dumeril [11] in 1807. Excellent historical surveys with recapitulations of the various terms which have been applied to these tumors are to be found in articles by Critchley and Ferguson,[12] Mahoney [13] and King.[14] In 1936 Mahoney [13] reviewed the literature and collected 142 cases of epidermoid, including the intracranial, diploic and spinal varieties. According to his figures the distribution of the neoplasm in these three situations, in the order named, is 16 : 3 : 1. In reports of large series of verified tumors of the brain [15] the incidence of epidermoids has varied from 0.2 to 0.6 per cent.

The outer membrane of an epidermoid often presents a distinctive mother-of-pearl appearance, a fact that led Cruveilhier [16] in 1829 to describe it under the term *tumeur perlée*. The structure is simple: An epithelial layer lying on a connective tissue base, which often attaches to pia mater,[17] lines the interior of the cyst, the contents of which are formed by desquamated, keratinized epithelium. Histologically the sac membrane, often 1 or 2 mm. in thickness, is composed of stratified squamous epithelium. There is often an abundance of cholesterol crystals in the contents of the tumor, although this is not always so. The nature of the growth suggested to Sir James Paget [18] the term "cutaneous

11. Dumeril, P.: Bull. Soc. Fac. de Med. **1**:32 (Feb. 19) 1807.

12. Critchley, M., and Ferguson, F. R.: Cerebrospinal Epidermoids (Cholesteatomata), Brain **51**:334-384 (Oct.) 1928.

13. Mahoney, W.: Die Epidermoide des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **155**:416-471, 1936.

14. King, J. E. J.: Extradural Diploic and Intradural Epidermoid Tumors (Cholesteatoma), Ann. Surg. **109**:649-688 (May) 1939.

15. Tooth, H.: Treatment of Tumors of the Brain and Indications for Operations, Proc. Internat. Cong. Med., London, 1913, sect. 11. Horrax, G.: A Consideration of the Dermal Versus the Epidermal Cholesteatomas Having Their Attachment in the Cerebral Envelopes, Arch. Neurol. & Psychiat. **8**:265-285 (Sept.) 1922. Mahoney.[13]

16. Cruveilhier, J.: Anatomie pathologique du corps humaine, Paris, J. B. Baillière, 1829, vol. 2, pt. I, plate 6.

17. Boström, E.: Ueber die pialen Epidermoide, Dermoide und Lipome und duralen Dermoide, Centralbl. f. allg. Path. u. path. Anat. **8**:1-98 (Jan.) 1897.

18. Paget, J.: Lectures on Surgical Pathology Delivered at the Royal College of Surgeons of England, London, Longmans, Green & Co., 1854, vol. 2.

proliferating cyst," although he did not restrict the designation to the epidermoid, applying it to the broader group of dermoids as well. It seems that the adoption of this term would be at once accurate, descriptive and final and would avoid the confusion that has attended the terminology of this tumor in the literature, and about which there is no definite agreement as yet.

Since the presence of an epidermoid situated intracranially is betrayed only by its pressure effects, or by altered flow of cerebrospinal fluid due to blocking of its route, one would not expect the true nature of the lesion to be suspected preoperatively. When such a tumor is exposed, the question should occur to the operator whether or not the mass visualized represents the entire extent of the tumor, since it has been shown that of 206 epidermoids located within the cranial cavity, 8 were situated in both the supratentorial and the infratentorial position. In the case just reported the original impression was that the tumor was in the posterior fossa, but plotting of the visual fields, together with the presence of dyspraxia and the history of convulsive seizures of long standing, displaced consideration of such a localization. The ventriculographic evidence was deemed consistent with the general picture presented by the patient. It was not, therefore, until the patient took a turn for the worse, after having made a start toward recovery after the first operation, and exhibited an accession of the so-called cerebellar signs that consideration was given to the possibility of a similar lesion's being situated in the posterior cranial fossa. Had the injected air entered the aqueduct of Sylvius it is probable that the presence of two tumors would have been demonstrated initially by aerography. Be that as it may, the predilection of these cysts for the regions of the basilar cisterns and their tendency to wind their way along the brain stem are points worthy of note when one is confronted with either a supratentorial or an infratentorial epidermoid.

SUMMARY AND CONCLUSIONS

1. A review of the literature revealed 205 cases of intracranial epidermoids.

2. Of this number, 7 instances have been recorded in which the lesion was situated in both the supratentorial and the infratentorial position, and to these the eighth example is added.

3. It is suggested that the term "cutaneous proliferating cyst" (Paget) would be an acceptable designation for the neoplasm now called epidermoid, or cholesteatoma.

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PSEUDOJACKSONIAN EPILEPSY IN CHILDREN

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An important advance in the treatment of so-called idiopathic epilepsy will be made if it is possible to break up the great army of epileptic persons, now regarded collectively as one group, into smaller, component groups, each with its own unique and constant clinical features, expressing its own individual etiologic mechanism and, finally, responding to its own specific method of therapy.

The first step in such a program must be the accurate description and delineation of all the various clinical syndromes as they are observed from time to time. Only after this can the etiologic factors and the appropriate therapy in any given case be determined. In 1936, in line with this thought, I described such a specific epileptic syndrome [1] which had come to my mind, and suggested a possible form of therapy. The present paper consists essentially of a description of a second specific epileptic syndrome, with an account of my experiences in attempting to determine its cause and to find a specific method of treatment. Unfortunately, these objectives have not been completely achieved, although the experiences, to date, suggest possible answers to these questions.

THE CLINICAL SYNDROME

The specific epileptic syndrome here described has been encountered only in children. The youngest child was 1½ years old when the seizures began; the oldest, 12 years of age.

The seizures are characterized by single or multiple, repeated "twitchings" or clonic "jerkings" of the extremities on one side of the body. These twitchings affect both the arm and the leg and start simultaneously in them. In sharp contradistinction to the true jacksonian seizure, they do not start from a focal point, such as the thumb or a finger or toe, and there is no "march" from one topographic cortical representation to another, which is such a fundamental characteristic of the focal convulsion as described by Hughlings Jackson; nor is there a crescendo with a peak of activity and then a falling off. The movements simply start abruptly, continue for a while with even intensity

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1. Scarff, J. E.: A Specific Epileptic Syndrome Relieved by Lysis of Pacchionian Granulations, Arch. Neurol. & Psychiat. **36**:373-375 (Aug.) 1936.

and stop. They never spread to the extremities of the opposite side, no matter how long they are sustained on the one side. Nor does the patient ever lose consciousness, bite his tongue or become incontinent.

The duration of the attacks ranges from three or five seconds to five or six minutes. The frequency of the seizures varies from two or three to as many as forty or fifty daily, but for each individual patient the frequency, once established, remains surprisingly constant day after day. Neither phenobarbital nor dilantin has any appreciable anticonvulsive effect on the seizures.

Hemiparesis on the side of the seizures developed at one time or another in each of the patients studied. The children who had right-sided paresis usually also suffered some aphasia. Psychometric tests were done on 6 of the children. The mental rating for 1 child was far below the normal level; a boy, who was very sick at the time the tests were made, was rated as normal; the remaining 5 children were given "very superior" mental ratings. The pneumoencephalograms revealed mild, diffuse cerebral hypoplasia (or atrophy) on the affected side in 6 of the 7 patients. Electroencephalograms, which were taken on 5 of the 7 children, showed a strikingly constant mixture of large, slow waves, with fast, "spiky" waves.

PATHOLOGIC DATA

The observations on cerebral exploration were inconstant, and hence disappointing. Subarachnoid fluid was excessive in 4 cases. The gyri and sulci were essentially normal in all cases. Pacchionian granulations appeared unusually dense in 4 cases. In 1 instance there was a small calcified mass of scar tissue, 1 cm. in diameter and about 1.5 cm. beneath the surface of the precentral gyrus, in the arm area of the right hemisphere.

Electrical stimulation of the cortex was performed in all 7 cases. The cortex was extremely refractory in 2 cases, gave normal focal responses in 3 cases and responded with convulsions in 2 cases when stimulation was applied in the vicinity of the particularly dense pacchionian granulations.

Electrocorticograms were made in 3 cases. These were normal in 1 instance but showed abnormal potentials in the other 2 as the superior mesial border of the hemisphere was reached.

No autopsies were performed in this group.

SURGICAL PROCEDURES AND RESULTS

No therapeutic measure was attempted on the exposed brain in cases 2 and 3, as none was indicated. In 1 of these cases the course continued to be progressively downhill, while, curiously, in the other the child made an almost complete, spontaneous recovery.

Large, dense, anomalous pacchionian granulations were divided in 4 instances (cases 1, 4, 5 and 6), the brain thus being freed of this rigid attachment along the superior mesial border of the hemisphere. The rationale exercised in this procedure is that previously described by me in 1936,[1] namely, that in brains having constitutionally low thresholds for stimulation the constant tug of unyielding pacchionian attachments between the cortex and the vault may be an irritating factor in the same manner as adhesions sufficiently strong to stimulate the production of convulsions. In each of these 4 cases the granulations were unusually dense. In cases 5 and 6 the excitability of the cortex to electrical stimulation increased notably as the region of attachment of the pacchionian granulations and the cortex was approached. In both these instances pronounced improvement in symptoms followed operation. Of the other 2 cases in which the granulations were divided, there was improvement in 1 (case 1) and a striking, progressive downhill course in the other (case 4).

In the last, but probably the most important, case of the series (case 7) a small calcified cicatrix, about 1.5 cm. in diameter, situated about 1 cm. below the surface of the precentral gyrus and close to the superior mesial border of the hemisphere, was excised. The boy has not had a single convulsion since the operation, nearly three years ago, and this in spite of the fact that he has taken no drugs for the last year. Moreover, the left hemiparesis, which was nearly complete prior to operation, has cleared up almost entirely. This boy now attends school regularly and participates freely in all sports on an equal footing with the other boys.

REPORT OF CASES

CASE 1.—J. B., a boy 4 years old, born Feb. 14, 1935, in May 1937, when he was a little over 2 years old, while suffering from a severe cold, had a generalized convulsion lasting eighteen minutes. Six months later, one year before admission, he began having seizures characterized by sudden stiffening of the body and extremities, with the head thrown back and the eyes turned to the right. These seizures occurred at first about once a month. A year later, about December 1937, the character of these seizures changed. They increased in frequency, were limited almost entirely to the right arm and leg and became more jerking and clonic in character. They lasted only a few seconds, during which time the child might be momentarily unconscious. When the seizure was over, he usually resumed his play immediately, and there never was tongue biting or incontinence. These new seizures occurred on the average of five to six times daily. Simultaneously with this change in the seizures, rapidly progressive weakness appeared in the right arm and leg and the right side of the face, and three months later aphasia developed. After a few weeks there was decided improvement in the hemiparesis and the aphasia. Gradually, however, the signs and symptoms again returned, and on Oct. 5, 1939 the child was admitted to the Neurological Institute.

Psychometric examination showed pronounced mental retardation, although the rating was probably influenced by his aphasia. Pneumoencephalograms showed slight hypoplasia of the left cerebral hemisphere.

On October 21 exploration of the left cerebral hemisphere was carried out, with the patient under anesthesia induced by avertin with amylene hydrate supplemented by a local anesthetic. There was a considerable increase in fluid in the subarachnoid space, especially as the midline was approached. The convolutions and sulci appeared to be normal. The primary motor gyrus was identified by electrical stimulation, and after this electrocorticograms were taken from many areas. From most of the exposed brain normal rhythms and potentials were obtained, but as the points studied approached the midline atypical potentials appeared, characterized by slow waves (1 to 2 per second), high potentials and sustained plateaus. In this connection, it should be observed that the avertin anesthesia had been supplanted by very light ether anesthesia for a few minutes, during the elevation of the flap; so these "plateau" waves may have been due to a residual effect of the anesthesia. On the other hand, it should be noted that these abnormal potentials were present only near the superior mesial border of the hemisphere, from areas adjacent to pacchionian granulations. These granulations were divided empirically but on the rationale that they might be acting as adhesions to make the brain locally more irritable, and a small piece of cellophane was interposed. Closure was then carried out in the usual manner.

The postoperative course was encouraging, only one attack occurring between the operation and the time of discharge from the hospital. From October 1939 until April 1940, while receiving ¼ grain (15 mg.) of phenobarbital three times a day, the boy had no attacks whatever. The phenobarbital was then discontinued, and during the next two months the patient had an average of only one attack a week, in sharp contrast to the five or six daily seizures which he had suffered before operation.

Unfortunately, in July 1940 the family moved to the Pacific coast, and contact with the child had been completely lost since then.

Case 2.—J. K., a boy 4 years old, born in June 1936, developed normally until November 1938. When he was a little over 2 years old an unexplained fever (temperature, 106 F.) developed, during the course of which he had a generalized convulsion lasting several minutes. During the next two years he had a generalized convulsion about every three months.

On Feb. 21, 1940, however, the patient had four seizures, all confined to the right side, consisting of twitchings of the right arm and leg and the right side of the face and turning of the head to the right. These lasted from one to four minutes. Apparently, the initial movement appeared always in the thumb and index finger but spread almost instantly to involve the entire right side of the body. It could not be definitely ascertained whether or not the patient was entirely unconscious during the attacks, but it is thought not, for immediately after the seizures he would get up, rub his left eye, complain of pain in it and then resume play. After the abrupt onset of these attacks he suffered three or four seizures daily.

On April 27, 1940 the patient suddenly became worse. On that date he had fifteen right-sided seizures, similar to those described, and on the next day thirteen. Simultaneously with this exacerbation there developed severe spastic weakness of the right arm and leg, so that the child dragged his leg in getting about. During the next month these attacks continued to occur many times daily, in spite of administration of 2 to 4 grains (0.13 to 0.26 Gm.) of phenobarbital daily, and the paresis increased. On June 10 the right hand was completely paralyzed, and the right leg was held in constant spastic extension. There was considerable aphasia.

The pneumoencephalograms were normal. The electroencephalograms showed grossly pathologic high voltage, slow waves, with a frequency of 1 to 6 per second, over both hemispheres. Faster spike components, with a frequency of 10 to 20 per second, were also often observed. These spike formations were more frequently seen over the right hemisphere, while the large, slow components favored the left.

On June 13, with the child under anesthesia induced by avertin with amylene hydrate, a large osteoplastic flap was turned up on the left side. The cortex appeared normal in all respects. Cortical stimulation was carried out, with an interrupted current of 2 volts at a frequency of 60 cycles per second. Response was obtained from only a single point, and this appeared to be primarily sensory. Each time a certain point, presumably in the postcentral gyrus, was stimulated, the patient would cry out sharply and move his right hand and arm in a voluntary fashion.

Electrocorticograms were then made from forty points on the exposed cortex, which were numbered and photographed. These tracings showed diffuse electrocortical dysfunction involving the tested areas of the exposed cortex, but maximal near the superior border of the hemisphere, in what was taken to represent the primary motor area for the upper extremity.[2] These observations have been reported in detail in another article.[3] Extirpation did not appear justified; hence the exploration was brought to a close without any therapeutic measure being carried out.

At the time of discharge from the institute, on June 23, the patient's status was essentially the same as it had been before operation; that is, he was severely hemiparetic on the right side of the body and almost totally aphasic. He was placed under treatment with phenobarbital, 0.090 Gm. daily, but during the second day at home he had seven seizures. For this reason the dose of phenobarbital was increased to 0.150 Gm. daily. During the next six to eight weeks he suffered six to eight attacks daily. After that the attacks gradually lessened in frequency and severity. From September 1940 to February 1941 he had only three seizures. At this time the amount of the drug received was reduced to 0.060 Gm. (on some days only 0.030 Gm.) daily. Between February 1941 and May 1941 he had no attacks.

I last saw this patient on Oct. 27, 1941. At this time he showed amazing and baffling improvement. Both the right hemiparesis and the aphasia had disappeared completely. He was bright, active and talkative. Since May 1941 he had been taking 0.060 Gm. of phenobarbital daily, and during this time he had not had a single convulsive episode.

CASE 3.—F. F., a boy aged 3 years 9 months, was first seen at the Neurological Institute in March 1938. He had had a normal birth and had been apparently well until November 1937, when he was about 2½ years of age. At that time there was an abrupt onset of seizures, which consisted of transient twitching of the left orbicularis palpebrarum muscle and of the left arm, lasting only two to three seconds. In the arm the movements consisted simply of sudden flexion of

2. Scarff, J. E.: Primary Cortical Centers for Movements of Upper and Lower Limbs in Man: Observations Based on Electrical Stimulation, Arch. Neurol. & Psychiat. **44**:243-299 (Aug.) 1940.

3. Scarff, J. E., and Rahm, W. E., Jr.: The Human Electrocorticogram, J. Neurophysiol. **5**:418-426 (July) 1941. (Detailed case records published with reprints.)

the fingers, wrist and elbow. These isolated jerkings recurred as often as once every twenty to thirty minutes. There was no loss of consciousness, tongue biting or incontinence during the attacks. Coincident with the onset of these seizures, there began a slowly developing spastic weakness of the left arm and leg, which caused him to drop objects from his left hand and to drag his left foot. He seemed to be unusually intelligent and likeable. Psychometric tests showed him to be of superior intelligence.

The roentgenograms were normal. The pneumoencephalogram showed slight generalized cerebral hypoplasia, possibly more pronounced on the right side. Electroencephalograms showed large, slow pathologic waves (1 to 5 per second), generally over both hemispheres, together with intermittent fast spikes (12 to 20 per second). These various pathologic components were all noticeably lateralized to the right side of the brain.

On May 25, 1939, with the patient under anesthesia induced by avertin with amylene hydrate supplemented with a local anesthetic, the right cerebral hemisphere was explored as far superiorly as the mesial border. There was more subarachnoid fluid than is normally present. Nothing else of apparent significance was noted. Electrical stimulation of the cortex was attempted with a faradic current from an induction coil, but, although a strong current was used, the entire hemisphere was extremely refractory and only one motor point, that for the fingers, could be identified. Electrocorticograms were not being made at this time. Since exploration had yielded no indication for further procedure, closure was made.

The immediate postoperative convalescence was uncomplicated, and the child was discharged on June 6, 1939, with instructions to take 0.030 Gm. of phenobarbital three times a day. Under this therapy, the attacks occurred with the same frequency and severity (at times every twenty minutes) as they had previous to the operation without the drug. Accordingly, in April 1940 phenobarbital was discontinued and dilantin, 0.1 Gm. twice a day, was substituted. After this the patient improved somewhat. He was last seen in April 1941, at which time he was having attacks similar to those previously suffered, but occurring never more than three times a day and often not at all for a week or two. The paresis, however, had slowly progressed. The entire left side of the body was hypoplastic and spastic. The arm was held flexed at the elbow and wrist, with marked loss of power. The leg was much less involved. Curiously, though, there was transient clonus of both legs, with a persistent Babinski sign on the left and an equivocal one on the right.

Case 4.—L. R., a boy 4 years old, had an unexplained fever (temperature of 102 F.) in March 1939, without apparent immediate sequelae. In June 1939 he suddenly began to have spells characterized by pain in the arm, followed almost immediately by extension of the right arm and the right leg, occasionally accompanied by a few mild clonic movements. The child fell but did not lose consciousness and usually cried. Such an attack lasted about five to ten seconds. When the extremities relaxed, the child would stop crying and say, "I feel okay now," and resume his play. The entire episode required about fifteen to twenty-five seconds. These attacks occurred about six times daily.

When he was first admitted to the Neurological Institute there was no paresis of the affected side and the reflexes were essentially normal, both before and immediately after an attack. But after about ten days there appeared slight weakness of both the right arm and the right leg, and this increased rapidly into pronounced right spastic hemiparesis. Psychometric tests gave the child a very superior rating.

Roentgenograms of the skull were normal. Pneumoencephalograms revealed slight hypoplasia of the left cerebral hemisphere. Electroencephalograms suggested a convulsive disorder with a focus in the right frontal and motor region, more frontal than motor.

A right craniotomy was performed on July 26, 1939, with the patient under anesthesia induced by avertin with amylene hydrate supplemented by a local anesthetic. The exposed cortex was hyperemic; the gyri were narrow and the sulci widened. There were lakes of cerebrospinal fluid between many of the gyri. Cortical stimulation was carried out with faradic current, and the primary motor areas for the upper extremity were identified. Electrocorticograms taken from these varied points were essentially normal. Unusually dense pacchionian granulations were present along the superior mesial border of the hemisphere, both in the superior portion of area 6 a-β and posteriorly in area 5, and these were divided, for reasons which will be discussed elsewhere.

The immediate postoperative course was uncomplicated, but there continued to be steadily progressive right hemiparesis, which at the time of his discharge, on August 12, was pronounced. He was still having five to ten right-sided seizures daily.

The patient was seen on Nov. 20, 1940, at which time he had almost an athetosis of the right arm and hand, and when he walked he lifted his right leg high and slapped his foot, flail-like, to the ground. He was fairly bright. He had been taking phenobarbital, 0.030 Gm. three times a day, under which regimen he had had no convulsive seizures during the daytime for eight months, although he was having some at night.

The child was last seen on April 17, 1941. At that time he was suffering from right hemiparesis with severe spasticity and, in addition, was beginning to experience transient spastic states in the left arm and leg. He was unable to stand or even sit alone. He appeared doped and would have fallen off his chair had he not been supported by his mother. These findings suggested progressive, bilateral, degenerative disease of the brain, or possibly some rare neoplasm. The mother was advised to bring the child for further studies, to include pneumoencephalographic examination, but she refused. She has also refused to bring the child back to the clinic for reexamination.

CASE 5.—E. M., a girl 7 years old, born in January 1932, was apparently well until November 1937, when she was 5 years old. At that time she had a generalized convulsion while at school. Seizures were present intermittently for four and a half hours. The patient was unconscious during this time. After the general seizure ceased, twitchings of the right side of the face persisted for some time. After this episode, the patient was well for ten months, until Aug. 6, 1938, when she was awakened from a sound sleep with "twitchings" of the right arm and leg, which lasted for five minutes. These recurred at frequent intervals during the next twelve hours and thereafter with decreasing frequency during the next seven to eight days, after which the patient again seemed well. However, in October 1938 she began to experience "twitchings" of the right leg below the knee, lasting two to three minutes and recurring three to four times daily.

By April 1939 these spells had increased greatly both in severity and in frequency. The "shaking" spells had originally involved only the leg, but now affected also the arm. They lasted five to six minutes at a time and were so violent as to make the bed shake. During all of this time the left side of the body remained entirely unaffected; there was no incontinence, and the patient remained entirely conscious throughout. These shaking spells recurred almost continuously, with only a few minutes between them, for four to six days at a stretch, and then the

patient might have none at all for seven to fourteen days. Lately, between attacks, there had been isolated, single simultaneous twitchings of the right arm and the right leg. Phenobarbital, 0.03 Gm. three times a day; calcium lactate, 0.6 Gm., and a high fat and low fluid diet were all tried, but this situation had obtained without much variation for six to eight months, when she was finally admitted to the Neurological Institute on April 13, 1939.

Since November 1938 the parents had noticed an increasing tendency to drag the right leg in walking and to stumble. There appeared to be no weakness of the upper extremity. After attacks, however, speech was often confused and unintelligible.

The results of neurologic examination were entirely normal except for ankle clonus on the right side. There were normal plantar responses bilaterally. The child was pleasant, and psychometric tests revealed normal intelligence for her age.

Pneumoencephalograms revealed a moderate degree of cerebral hypoplasia, more pronounced on the left. Electroencephalograms were characterized by extremely large, pathologic slow waves, at a rate of about 2 per second, appearing generally over both hemispheres but distinctly lateralized to the left. On the left side these slow waves showed foci ranging anteroposteriorly from the postcentral area into the anterior portion of the frontal lobe; they were larger over these regions than more posteriorly, over the occipital lobe and the parieto-occipital area. Along with the slow delta waves, a spike component was often noted, resulting intermittently in large wave-spike contours. The pattern indicated diffuse cortical involvement, much more extensive on the left side.

On April 15 exploration of the left cerebral hemisphere was performed with the patient under anesthesia induced by avertin with amylene hydrate supplemented with a local anesthetic. There was slightly more subarachnoid fluid than is usually seen at operation, but the gyri and sulci appeared normal. The entire superior mesial border of the hemisphere was involved, with an unusually dense plexus of veins passing into the superior longitudinal sinus, and these, in turn, were bound up in peculiarly dense pacchionian granulations. Stimulation of the cortex with weak currents obtained from the thyratron stimulation produced isolated movements from the various primary motor areas of the upper extremity, but as the superior mesial border of the hemisphere and the dense pacchionian granulations associated with it were approached, stimulation at various points with even a weak current produced abrupt, powerful mass movements of the entire lower extremity, suggesting movements which the limb might assume in locomotion. This region appeared hyperirritable to stimuli, and on the chance that the dense attachments between cortex and dura afforded by the pacchionian granulations might be contributing to this irritability, I divided them and interposed a small piece of cellophane between the divided ends of the veins and granulations. Closure was then made in the usual manner.

The postoperative course was uncomplicated. The child was placed under treatment with phenobarbital, 0.015 Gm. three times a day. At the time of discharge she seemed definitely better than before operation. There was a progressive reduction in the number of "twitchings" of the right leg, and for five days prior to discharge there had been none at all. The gait, too, was much improved, and the spasticity of the right leg appeared to be much less than before operation. There was, however, very slight twitching of the right side of the mouth. She was last seen on April 29, 1940, about one year after operation. At that time she was still taking phenobarbital, the same dose as before. During the year just ending she had had seizures similar to her severe preoperative attacks on

only two occasions. In October 1939 seizures occurred during a period of about a week, gradually subsiding spontaneously. About April 10, 1940, she had several attacks during a three day period, but these were mild. She was still bothered by momentary, single "ticlike" twitchings of the left eyelid, but on the whole she was much better than she was before operation.

CASE 6.—J. T., a girl aged 19 years, was admitted to the Neurological Institute in May 1939, complaining of seizures involving the right side. In 1932, when 12 years old, she began to experience episodes during which she suddenly became inattentive and unresponsive, usually with simultaneous twitching of the right leg and arm. Sometimes there was almost no twitching; at other times there were rather severe jerking movements, involving the face as well as the arm and leg. As a rule, these attacks lasted twenty to thirty seconds; the left side of the body was not involved, and the patient did not lose consciousness. These attacks recurred four to eight times during twenty-four hours, or several weeks might pass without them. In addition to these attacks, since 1934 the patient had had each year from one to three true jacksonian convulsions, starting with coarse, clonic movements in the right arm and spreading in typical fashion to the right leg, accompanied by loss of consciousness, incontinence and biting of the tongue. During the past year she had been receiving dilantin, 1 capsule (0.1 Gm.) three times a day, and phenobarbital, 0.06 Gm. three times a day.

Examination at the time of admission revealed nothing abnormal except for slight hyperreflexia and a Babinski sign and slight reduction of stereognostic sense on the right side. The patient was naturally left handed. Psychometric tests showed her to be of very superior intelligence. Pneumoencephalograms revealed mild cerebral hypoplasia on the right (!) side.[4]

On June 8, 1939, with the use of local anesthesia, extensive exploration of the left cerebral hemisphere was performed. The gyri and sulci appeared to be normal; there was no excess of subarachnoid fluid.

Electrical stimulation with the thyratron gave sharply focal responses along the motor gyrus, which was easily identified throughout its length. At the junction of the precentral and postcentral gyri with the superior mesial border of the hemisphere there were unusually large, dense pacchionian granulations accompanying a plexus of veins, which were remarkably large and numerous. Electrical stimulation with weak current at the superior border of the hemisphere produced a generalized convulsion, beginning with abduction of the arm and subsequently resembling somewhat the pattern of the clinical seizures seen before operation. Because the clinical evidence pointed to this region and the pacchionian granulations lay in an anatomically acceptable area and, finally, because stimulation at this point produced the only convulsion obtained, and one which did, in fact, resemble somewhat the preoperative clinical seizures, it was felt that there were sufficient indications for dividing these granulations. Accordingly, this was done, and the divided ends were separated with Cargyle membrane. Closure was then made in the usual manner.

The postoperative convalescence was uneventful, and the patient was discharged on June 21. She was last seen on May 25, 1941, almost two years after operation. During the six months just ended she had been taking dilantin, 1 capsule three times a day, and phenobarbital, 0.030 Gm. twice a day, somewhat less medication

4. Casamajor, L.; Smith, J. R.; Constable, K., and Walter, C. W. P.: The Electroencephalogram of Children with Focal Convulsive Seizures, Arch. Neurol. & Psychiat. **45**:834-847 (May) 1941.

than she had received preoperatively. She had experienced none of the severe jacksonian seizures with loss of consciousness since her operation two years before, and the minor twitching episodes of the right arm and leg had been greatly reduced in severity and decreased to one-half their former frequency.

CASE 7.—R. G., a boy 8 years old, was admitted to the Neurological Institute in May 1939. At the age of 17 months he began to have tremors and jerking movements of the left arm, which lasted for only a few seconds. The spells recurred without change from the time the patient was 17 months until he was 5 years old. At the age of 5, however, the left leg stiffened each time the arm jerked. There was never any loss of consciousness. These seizures lasted for only a second or two. They might occur two to three times a day, or several weeks might pass without any attacks. During all this time the patient was receiving systematic phenobarbital therapy, under a physician's direction, without apparent relief.

Weakness of the left arm and hand was also noticed by the mother at the same time that the aforedescribed jerkings first appeared. No weakness of the left

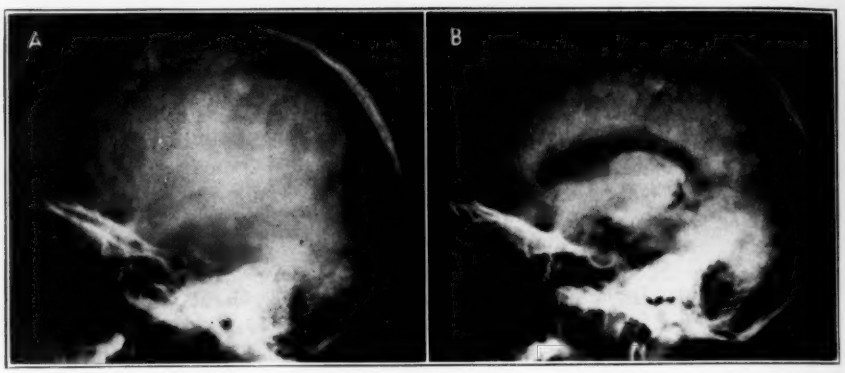

Fig. 1 (case 7).—*A*, preoperative roentgenogram of the skull, showing the position of the calcified subcortical cicatrix, about 1.5 cm. beneath the surface of the brain and about 1.5 cm. from the midline. The patient, a 12 year old boy, had had convulsions since he was 1½ years old. *B*, preoperative pneumoencephalogram. Note how the roof of the lateral ventricle has been pulled upward by the calcified subcortical cicatrix. In addition to the convulsions, severe, progressive left hemiparesis was developing prior to operation.

leg was noted at that time, but when the boy first began to walk, at 17 months of age, it was observed that he dragged his left leg.

The conditions just described persisted without essential change in character or degree until October 1938, seven months before the present hospitalization, when the patient was approximately 7½ years old. At that time, however, the character of the spells changed drastically. In these new spells the patient first lost consciousness and the body stiffened; the head turned to the right; the right side of the face started to contract, and the right arm was abducted. In short, there occurred a typical jacksonian seizure followed by generalized convulsions. From October 1938 until May 8, 1939 this boy had had three or four such attacks daily.

Simultaneously with the increase in severity of the attacks, there occurred a decided increase in the left hemiparesis. When admitted, the patient could hold nothing in his left hand and could not bear any weight on his left foot, but dragged it behind him. Psychometric tests showed that the patient functioned at a low average mental level despite his great physical disability.

Electroencephalograms revealed abnormal, large, slow waves, with a rate of 2 to 6 per second, together with wave-spike contours, with a frequency of 2 to 3 per second, over the central and postcentral areas of the right cerebral hemisphere and, to a lesser degree, over a similar portion of the opposite hemisphere.

Plain roentgenograms of the skull showed a small deposit of calcium, about 1 cm. in diameter, in the right central region, about 1 to 2 cm. to the right of the midline and about 1 to 2 cm. below the surface of the cortex (fig. 1). The pneumoencephalograms showed an outpouching of the right ventricle toward the region of the calcific deposit just referred to, which indicated that the latter was a scar.

On June 19, 1939 a right parietal craniotomy was performed, the primary motor gyrus incised and a subcortical, calcified cicatrix removed. By precise

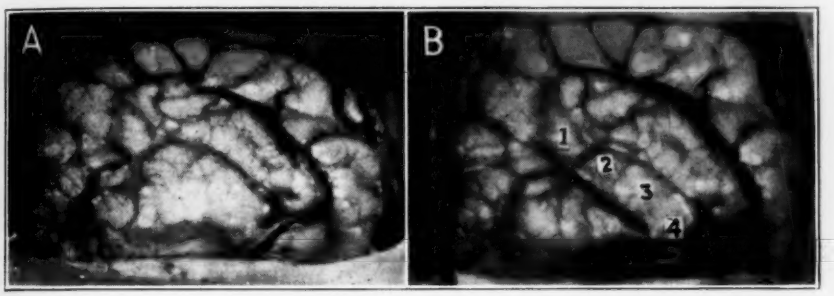

Fig. 2 (case 7).—*A*, the normal-appearing right cerebral cortex as first exposed at the operating table (retouched). *B*, the same area after excision of a calcified subcortical cicatrix (retouched). The numbers indicate primary motor points for the upper extremity as identified by electrical stimulation. The dark line anterior and parallel to the numbers is the incision in the cortex through which the cicatrix was removed.

measurements from suture lines, as revealed in the roentgenograms, and on the skull itself, a point on the surface of the brain was determined which, it was felt, was situated directly over the calcific deposit seen in the roentgenograms. Electrical stimulation of the cortex then revealed that the point lay directly on the primary motor gyrus in the hand area. With considerable trepidation this gyrus was incised lengthwise for a distance of 2 to 3 cm. and to a depth of 2 to 3 cm. Here I found a firm, irregular, calcified cicatrix, which I removed.

The immediate postoperative course was fairly smooth, and the patient was discharged on the thirteenth day. He has had no attacks of any sort during the nearly three years since the operation, in spite of the fact that he long ago stopped taking any medicament. In addition, there has been an entirely unexpected and considerable improvement in motor power and general use of his left arm and leg. His mother states that he is constantly on the go and that he is able to "lick both of his brothers at either wrestling or fighting."

COMMENT

The primary purpose of this paper has been to describe for the first time a second [1] specific epileptic syndrome thus far observed only in children. To facilitate and provoke discussion, I have called it "pseudojacksonian" epilepsy of childhood.

The cause and the pathologic mechanisms behind the clinical syndrome, unfortunately, are not yet clear. Experience with these cases, however, suggests two mechanisms for consideration. The first is that anomalous pacchionian granulations may produce irritation of a brain with a constitutionally low threshold somewhat as do adhesions, thus acting as a "secondary trigger mechanism" in releasing convulsive phenomena.[1] This was the working hypothesis utilized in management of some of the earlier cases in the present series.

The simultaneous and equal involvement of the arm and the leg on one side in rhythmic, repetitious and sometimes well sustained movements early suggested to me that these movements might represent fragments of some more complex action pattern having to do with locomotion, possibly even a vestige of a phylogenetically earlier manner of propulsion, such as quadrupedal walking or swimming.

The Vogts, in 1926, pointed out that strong stimulation of area 6 a β, near the superior mesial border of the hemisphere, would result in simultaneous mass movements of the two opposite extremities, and Foerster, in 1936, reported similar mass movements resulting from stimulating the superior border of the hemisphere not only anterior to the central sulcus (area 6 a β) but posterior to it (area 5). Both of these areas, it will be noted, are the regions where the larger pacchionian granulations are located.

If anomalous pacchionian granulations were to provide irritative stimuli to the brain, it is evident from the foregoing discussion that the irritation might easily fall on area 6 a β or area 5 and thus set off the mass movement of the contralateral arm and leg, described by Vogt and Vogt in animals and by Foerster in man. Under these circumstances, lysis of the granulation, with release of the brain, might remove the irritative stimuli to the brain which were causing these movements. It was this reasoning which led me to divide the pacchionian granulations in 4 of the cases.

The results of dividing the pacchionian granulations gave some support to the aforestated thesis. In 3 of the 4 cases in which this treatment was employed there was definite improvement, and this was most evident in the 2 cases in which electrical stimulation of the cortex revealed hyperirritability in the region of the granulation and in which the electrocorticograms showed dysfunction. In the fourth case, in

which division of the granulations failed to result in improvement, there had been no indication for the division other than the appearance of the granulations.

A second mechanism is suggested in the last case (case 7). Here I was fortunate in having the identity and the precise location of the etiologic factor, a subcortical cicatrix, revealed in the roentgenogram, since the lesion was calcified. It is highly significant that this cicatrix was close to the area held under suspicion during my long struggle with the first 6 cases, namely, the region close to the superior mesial border of the hemisphere and to the primary motor cortex.

It is important to note that this lesion was entirely below the surface layers of the cortex. Whatever the pathologic and physiologic significance of this may be, its clinical and surgical significance is great, for this type of lesion would never be found by inspection of the exposed brain alone.

The results of treatment in case 7 were so strikingly successful that it is evident that this case probably holds the key to the specific treatment of this particular syndrome. Although one can only speculate, it seems likely that a similar cicatrix was the basic etiologic factor in the 5 preceding cases (except case 4), the lesion being missed because it was not calcified. If this is true, then the role of the pacchionian granulations was simply one of tugging on and irritating the brain at a point where it had already become locally hyperirritable owing to the presence of an active subcortical cicatrix, and they thus served as secondary activating mechanism. Technical problems are inherent in the fact that the lesion is subcortical. It is probable that the seat will have to be sought for at the operating table with a bipolar electrocorticograph, much as one seeks metal buried beneath the ground with electromagnetic indicators.

There remains the final question as to the origin of the cicatrix itself. Unfortunately, on this point I have no data, or even good speculations. The physiologic effect of the cicatrix is worth a few words, however. It should be noted that the boy in case 7 had almost complete hemiparesis before operation. Despite the trauma incident to a longitudinal incision, ½ inch (1.27 cm.) long and 1½ inches (3.8 cm.) deep, splitting the primary motor gyrus, plus the trauma incident to the excision of the irregular cicatrix, the hemiparesis cleared up almost completely after the cicatrix was removed. I can explain this only by assuming that the scar must have been constantly irritating and have produced some edema about it, which impeded the function of the affected area of the brain, much as occurs with a glioma. With the removal of the irritating lesion the edema subsided and the surrounding brain could function normally.

SUMMARY

An apparently specific epileptic syndrome occurring in children is described. It consists of repeated clonic jerkings of the extremities of one side of the body, starting abruptly and simultaneously in the arm and the leg, without "march" or loss of consciousness. The attacks occur with a rather constant frequency in each case, several to many times daily.

Hemiparesis on the side of the seizures developed at one time or another in each of the cases studied.

Pneumoencephalograms revealed mild diffuse hypoplasia of the affected brain in 6 of 7 cases. In 1 case a subcortical calcified, degenerated area was revealed. Pacchionian granulations appeared unusually dense in 4 cases.

Treatment with phenobarbital or dilantin was usually without effect on the seizures.

Lysis of the abnormal pacchionian granulations produced decided improvement in 3 of 4 cases, and removal of the calcified mass gave relief from both seizures and hemiparesis in another case.

Dr. Byron Stookey gave permission to use case material from the neurosurgical service of the Neurological Institute and assisted in the preparation of this manuscript.

Neurological Institute of New York.

MIDBRAIN DEAFNESS

TUMOR OF THE MIDBRAIN PRODUCING SUDDEN AND COMPLETE DEAFNESS

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The following case of tumor of the midbrain is reported because it presented an unusual symptom, namely, sudden and complete deafness. Not many reports of this condition have appeared in the literature, and since the disorder is uncommon enough to be overlooked, even in the presence of other localizing signs of a lesion of the midbrain, the report of a single case seems warranted. Neighborhood symptoms, such as hypersomnolence, mental changes and palatal paralysis, were also present, but were not sufficiently outstanding to require special mention, particularly since their significance is well recognized.

REPORT OF A CASE

History.—C. R., a white man aged 55, was admitted to the Mount Sinai Hospital on Oct. 11, 1940 with a history of impairment of hearing of eighteen months' duration. At the time of the onset it was said that he complained of weakness and pain in the legs. There had also been increasing loss of sexual potency. The patient was nevertheless able to carry on his daily occupation until about two weeks prior to admission. At that time his wife noticed that he slept most of the time and that it was difficult to arouse him.

One of us (M.S.) had been treating the patient at various intervals for impairment of hearing. It was found that the drums were retracted and that catheterization of the eustachian tubes afforded the patient some relief from his "stuffed head." The deafness, however, was not of the conduction type, and nasopharyngoscopy and diagnostic catheterization disclosed no abnormalities about the eustachian tubes. An audiometer test done one week prior to admission showed a hearing loss of 40 to 60 decibels at the higher tone levels, whereas the impairment in the lower tone range was only 20 to 30 decibels. It was evident that the neural mechanism of hearing was definitely at fault. The vestibular nerve, however, appeared not to be involved. As the patient's history disclosed that he had been imbibing considerable quantities of bootleg alcohol, the possibility of toxic neuritis of the cochlea was considered, and a preparation of the vitamin B complex was prescribed. When the patient, however, suffered sudden complete

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loss of hearing and nystagmoid movements of the eyes were noted, an organic lesion of the brain was suspected, and the patient was admitted to the Mount Sinai Hospital for study.

Examination.—On admission the patient seemed to be resting comfortably and offered no subjective complaints. The drowsiness described by his wife was not observed at this time. The temperature, pulse and respiration were normal. The pupils were round, equal and regular; they reacted sluggishly to light and better in accommodation. The extraocular movements were normal. There were a few nystagmoid jerks during rotation of the eyes in all directions. Hearing was lost to both high and low notes, and there was absence of bone conduction bilaterally. The audiometer test revealed complete loss of hearing in both ears. External examination of the ears demonstrated old tubal catarrh, which was considered insufficient to account for the deafness. There was drooping of the right side of the soft palate, and the gag reflex was absent bilaterally. Both knee jerks were absent. The bladder was distended.

Two days later the patient's cerebration was found to be slow and out of proportion to the degree of his deafness. At this time the pupils were unequal, the right being larger than the left. Neither pupil reacted to light or on convergence. Spinal tap disclosed a pressure of 130 mm. of water. A Bárány examination was attempted but was unsuccessful because of the patient's mental hebetude.

Course of Illness.—Within a week the mental dulness had progressed to a state of complete stupor with incontinence. It was difficult to arouse the patient for his meals, but when he was finally awakened he seemed to be alert and cooperative. A few days later, however, his responses became irrelevant, and he seemed to be confused. He tended to perseverate and had no recollection of recent events. He was also abusive toward his wife. Dehydration by intravenous injection of sucrose was tried but had no effect on the patient's mental state. The fundi remained normal, and there was no increase of intracranial pressure on repetition of the spinal tap. At this time, weakness of the right arm was noticed, and the deep reflexes in this limb were increased.

Results of examination of the blood, urine and spinal fluid were without significance. Roentgen studies of the chest, mastoids and skull also failed to reveal any evidence of abnormality.

The patient's coma increased, and pulmonary edema developed, of which he died on October 28, seventeen days after admission.

Autopsy.—Autopsy, performed by Dr. David R. Meranze, pathologist to the Mount Sinai Hospital, revealed the following changes: moderate aortic atheroma, slight diffuse dilatation of the heart with fiber atrophy, marked passive congestion and focal edema of the lungs, congestion of the spleen with focal hemorrhage, cloudy swelling of the liver, subacute hemorrhagic cystitis and pronounced congestion of the kidneys.

Aside from the presence of a neoplasm in the brain stem, the brain showed no abnormalities. The tumor extended from the posterior part of the hypothalamus, and infiltrated the midbrain and pons, its tail projecting between the cerebellar hemispheres, hollowing out a shallow indentation in both hemispheres and compressing the dorsal aspect of the medulla. The tumor involved the entire tegmentum of the midbrain and pons, particularly on the left side. The aqueduct of Sylvius was displaced toward the right side without being blocked, so that it was possible to pass a probe through its entire length.

The microscopic examination of the tumor was made by Dr. Charles Davison, neuropathologist of Montefiore Hospital.

Sections of the hypothalamus, cerebellum and spinal cord were stained by the myelin sheath and hematoxylin-eosin methods. The myelin sheath preparations could not be made out well, as the paraffin sections did not take the stain well.

Hypothalamus.—There was a fairly large tumor mass, which had a varied histologic picture. With low magnification, clusters of cells having a slight papillomatous appearance were seen surrounding free spaces or blood channels, the cells being arranged in a radiating fashion. With higher magnification, the cells around these vascular channels appeared to consist of irregularly shaped, densely stained nuclei, with little cytoplasm. An occasional mitotic figure was noted. Between these dense collections of cells there was a looser tissue in which the cells consisted essentially of fibrillary astrocytes. An occasional protoplasmic astrocyte was also observed. In other regions there were a few strands of polar spongioblasts, which had a slight palisade arrangement. In still other regions there were cells with densely packed, deeply stained, irregularly shaped nuclei and little cytoplasm. Some of these could be identified as ependymal cells. Among these were also mitotic figures. The prevailing cells throughout the tumor, however, were fibrillary astrocytes.

Microscopic Diagnosis.—The diagnosis was mixed glioma, essentially astrocytoma or astroblastoma.

The diagnosis of astrocytoma was made essentially because of the numerous fibrillary astrocytes. The possibility of an astroblastoma was considered because of the arrangement of cells around the free spaces, but this could not be confirmed since no Cajal stains were made. In addition to the aforementioned glia cells there were spongioblasts, ependymal cells and atypical glia cells.

COMMENT

The outstanding feature of the case was the sudden onset of deafness in a man who had previously shown mild impairment of hearing. After otogenic causes had been ruled out, it was natural to assume that the condition was caused by involvement of the acoustic nerve. The association of fixed pupils and absence of knee jerks suggested syphilis of the central nervous system (tabes), but the results of serologic studies were negative. A lesion of the pons involving both trapezoid bodies was also suggested, but it was only after the patient began to show other evidences of cerebral involvement that the cause of the deafness was sought elsewhere.

As is well known, lesions which produce deafness as a rule involve the eighth nerve or its terminal filaments (Wilson [1]). It is less well known, however, that impairment of hearing may occur with lesions

1. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 1, p. 410.

of the brain stem. In the pons, for instance, it may result from involvement of the trapezoid bodies. The impairment in cases of such a lesion is more likely to be unilateral and incomplete, because the size of the pons enables many fibers to escape compression. Horrax,[2] in a study of 15 cases of pontile tumor, found severe bilateral impairment in 3 cases, unilateral deafness in 4 cases and questionable impairment in 1 case.

In contrast to these observations, Brunner, in his monograph,[3] described the syndrome of midbrain deafness in considerable detail and concluded that tumors of the tegmentum of the midbrain are more likely to give rise to sudden and complete deafness. This is due to the fact that the auditory pathways in this region, namely, the lateral lemnisci, the posterior colliculi, the brachia of the posterior quadrigeminate bodies and the medial geniculate bodies, are closely placed together in what has been described as the "isthmus acusticus." Such lesions are usually associated with descending degeneration in the cochlear system down to the spiral nerve of the cochlea. Moreover, the small size of the midbrain and the compactness of its tissues enable a tumor of moderate size to compress the auditory pathways on both sides, as well as to produce widespread functional disorder of other systems. According to Brunner, deafness due to a lesion in the midbrain is usually a late symptom and therefore has an unfavorable prognostic significance. As a rule, it shows an unusually rapid, almost apoplectiform, progression and is associated with marked shortening of bone conduction and labyrinthine hyperexcitability. He expressed the opinion that the latter change is important in the differential diagnosis of tumors of the midbrain and those occurring lower in the brain stem or in the cerebellum. In the latter areas there is early destruction of the secondary pathways of the vestibular nerves, so that diminished excitability of the labyrinth may be observed before there is any definite impairment of hearing. One-sided lesions give rise to contralateral deafness, since the pathways on each side are connected with the opposite ear. Brunner classified the various conditions which give rise to the syndrome as follows: (1) tumors of the tegmentum of the midbrain, caudal to the red nucleus; (2) tumors of the transition zone between the thalamus and the midbrain; (3) pinealomas; (4) suprasellar tumors, and (5) tumors of the quadrigeminate plate.

In the first of Brunner's cases, that of a woman aged 36, a tumor was observed occupying the posterior portion of the right thalamus and

2. Horrax, G.: Differential Diagnosis of Tumors Primarily Pineal and Primarily Pontile, Arch. Neurol. & Psychiat. **17**:179 (Feb.) 1927.

3. Brunner, H.: Otologische Diagnostik der Hirntumoren, Berlin, Urban & Schwarzenberg, 1936, chaps. 8 and 9.

infiltrating the right cerebral hemisphere, on the one hand, and the tegmentum of the midbrain, on the other. Clinically the patient presented the symptoms of drowsiness, pathologic attacks of sleep, flushing of the face, fixation of the pupils to light, paralysis of upward gaze, cerebellar signs, increased intracranial pressure, tinnitus and severe bilateral deafness, which came on rapidly within the space of ten days. Both labyrinths were found to be hyperexcitable.

In his second case a man of 30 presented inequality of the pupils with fixation to light, limitation of upward gaze, cerebellar signs, papilledema with secondary optic nerve atrophy, signs of increased intracranial pressure, left-sided deafness with subjective tinnitus and prompt response of the labyrinth to caloric stimulation. At autopsy a pinealoma was observed which filled the posterior portion of the third ventricle and infiltrated the quadrigeminate plate and the tegmentum of the midbrain. The left cochlear nerve showed degenerative atrophy, while the right one was normal.

In Siebenmann's [4] case a youth of 18 had a large gliosarcoma of the pineal gland, which had infiltrated the entire quadrigeminate plate, the tegmentum of the midbrain, the posterior portion of the third ventricle, the entire posterior half of the right pulvinar and the anterior portion of the cerebellum. The illness lasted twenty months. Five months after the onset the patient began to complain simultaneously of bilateral tinnitus and impairment of hearing. Hearing failed rapidly, so that one month later he was completely deaf. He also showed beginning optic nerve atrophy with diminished vision, complete paralysis of the extraocular muscles (exclusive of the rectus internus and rectus externus), accommodation paralysis of both pupils, anisocoria, lack of response to light, slowness of speech and apathy. There was loss of bone conduction, while air conduction was still present. Later air conduction was also lost. The microscopic studies in this case revealed that the primary cochlear nuclei and cochlear nerves on both sides were normal. Siebenmann stated that diminution of hearing could be ascribed to a tumor of the midbrain if (1) the deafness occurred together with other cerebral symptoms related to the tumor and (2) if the deafness showed a strikingly progressive character.

Siebenmann also summarized a number of similar cases previously reported in the literature. In all of them deafness became complete within four to eight months after it was first observed. Some of the other symptoms described in these cases were epileptic seizures, ataxia, speech disturbances, incontinence of urine, apathy, stupor, excitement, destructi-

4. Siebermann, F.: Ueber die zentrale Hörbahn und über ihre Schädigung durch Geschwülste des Mittelhirns speciell der Vierhügelgegend und der Haube, Ztschr. f. Ohrenh. **29**:28, 1896.

bility, amnesia and depression. In addition, hydrocephalus and evidences of increased intracranial pressure usually occurred early as the result of obstruction of the aqueduct. Pupillary changes and extraocular muscle palsies were frequently present, while tinnitus occurred but was not the rule.

Weinland's [5] case was that of a man of 25 whose illness lasted two years. Twenty months after the onset there was pronounced impairment of hearing on the right side, papilledema with beginning optic nerve atrophy, anisocoria, sluggish reaction of the pupils in accommodation, slow and difficult speech, amnesia and depression. Section revealed a glioma, the size of a walnut, situated over the left half of the quadrigeminate plate. The lateral lemniscus had entirely disappeared in the region of the left quadrigeminate plate and showed definite degeneration in the proximal portion of the pons. There was also round cell infiltration of both acoustic nerves.

Horrax and Bailey [6] found that in 5 out of 12 cases of tumor of the pineal body some degree of central deafness was present, being complete in 3 cases. They ascribed it to pressure on the inferior colliculi.

In the case of Harris and Cairns,[7] that of a young man of 20 with a pineal tumor, marked impairment of hearing developed on the left side twelve months after the onset of symptoms. This cleared up after removal of the tumor. They also ascribed the deafness to compression of the posterior quadrigeminate bodies.

The condition of the pupils in our case was the only localizing sign directly referable to the midbrain. On admission both pupils reacted sluggishly to light and better on convergence, and within a few days they became unequal and fixed. The absence of increased intracranial pressure was surprising, since it is well known that with tumors of the midbrain there is early blocking of the iter, with production of obstructive hydrocephalus. The absence in our case can be explained by the fact that the tumor had merely displaced the aqueduct to the right, without encroaching on its lumen, so that the occlusion was not complete. Thus, a probe could easily be inserted the entire length of the aqueduct. The evidences of bulbar involvement, namely, weakness of the palate and dysphagia, were apparently due to involvement of the bulbar nuclei by compression of the dorsal aspect of the medulla.

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5. Weinland, E.: Ueber einen Tumor der Vierhügelgegend und über die Beziehungen der hinteren Vierhügel zu Geistesstörungen, Arch. f. Psychiat. **26**:363, 1894.

6. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, Arch. Neurol. & Psychiat. **13**:423 (April) 1925.

7. Harris, W., and Cairns, H.: Diagnosis and Treatment of Pineal Tumors, Lancet **1**:3, 1932.

SUMMARY

A case is reported of sudden and complete deafness resulting from a glioma which infiltrated the tegmentum of the midbrain. The other localizing signs were the presence of sluggishly reacting pupils, which later became unequal and fixed, and pathologic drowsiness and mental symptoms resulting from involvement of the hypothalamus. In addition, extension of the tumor to the medulla gave rise to weakness of the soft palate and dysphagia. An unusual feature of the case was the absence of increased intracranial pressure. This was explained by incomplete occlusion of the aqueduct of Sylvius.

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ATYPICAL SEIZURES ELICITED BY ELECTRICAL STIMULATION OF THE CEREBRUM IN THE CAT

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Since the pioneer work of Fritsch and Hitzig [1] in 1870 and of Ferrier [2] in 1873, many investigators have stimulated the cerebral cortex of animals and of man. Most such experiments have been carried out with the brain exposed and the subject anesthetized, at least lightly, or controlled with local anesthesia. Talbert,[3] in 1899, using a method and (according to a recent personal communication) the very electrodes devised by Ewald,[4] reported the results of stimulation of the cortex of unanesthetized and unrestrained animals in whose skulls were implanted permanent electrodes. It is surprising that Talbert's work was for so long a time unappreciated, since work in this laboratory for several years [5] has indicated the value of implanted electrodes in cortical stimulation.

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1. Fritsch, G., and Hitzig, E.: Ueber die elektrische Erregbarkeit des Grosshirns, Arch. f. Anat., Physiol. u. wissensch. Med. **36**:300-332, 1870.

2. Ferrier, D.: Experimental Researches in Cerebral Physiology and Pathology, West Riding Lunatic Asylum Rep. **3**:30, 1873.

3. Talbert, G. A.: Some Experimental Studies in Cerebral Localization, Philadelphia M. J. **4**:1024-1029, 1899.

4. Ewald, J. R.: Ueber künstliche Reizung der Grosshirnrinde, Deutsche med. Wchnschr. **24**:180, 1898.

5. Clark, S. L., and Ward, J. W.: Electrical Stimulation of the Cortex Cerebri of Cats: Responses Elicitable in Chronic Experiments Through Implanted Electrodes, Arch. Neurol. & Psychiat. **38**:927-943 (Nov.) 1937. Ward, J. W.: The Influence of Posture on Responses Elicitable from the Cortex Cerebri of Cats, J. Neurophysiol. **1**:463-475, 1938. Clark, S. L., and Ward, J. W.: The Influence of Stimulus Strength and Duration on the Responses from Cortical Stimulation Through Implanted Electrodes, Am. J. Physiol. **131**:650-658, 1941.

Convulsions elicited in unanesthetized and unrestrained animals by electrical stimulation of fixed cortical points [6] were similar to jacksonian epileptic attacks in man. The animals exhibited rapid clonic movements of the extremities, which came in a definite order or march and were accompanied by evidence of visceral involvement. For a short time afterward the placing reactions were reduced or absent, in a manner comparable perhaps to the postseizure occurrence of the Babinski response as observed in man (Notkin, Coombs and Pike [7]). The extent of the convulsions and the pattern depended on the location of the electrode and the strength and the duration of the stimulus employed. Of some significance is the fact that the convulsions could be repeated from day to day in the same animal.

In several instances in the experiments described by Ward and Clark [6] an unexpected variation of the typical jacksonian seizure was observed (page 1223).

> [After a clonic seizure] the hindlegs appeared to be in a state of hyperextension, which caused the animal to walk almost on the toes, with the hindquarters well elevated; the forelegs were flexed at the elbows. On walking, stepping was exaggerated in the hindlimbs, with each foot lifted high in turn. In some cases only one hindlimb was involved.

The similarity of these movements to those observed after electrical stimulation of the cerebellar cortex in the unanesthetized cat [8] was evident. From the cerebellum seizures were obtained which showed three phases: the first, with the stimulus; the second, appearing as a rebound to the first, and immediately after the end of the stimulus, and the third, prolonged and involving the various parts of the animal in a series of relatively slow movements in a definite sequence lasting several minutes. This sequence of movements was further described as resembling a "slow motion" picture.

The present paper is concerned with similar "slow" seizures as produced by stimulation of the cerebral cortex of unanesthetized and unrestrained cats.

METHOD AND MATERIAL

The observations were made on a series of 84 adult cats which, while being used for other experiments, were prepared and stimulated in a similar manner. In 62 of these cats convulsive seizures were produced in the course of the experi-

6. Ward, J. W., and Clark, S. L.: Convulsions Produced by Electrical Stimulation of the Cerebral Cortex of Unanesthetized Cats, Arch. Neurol. & Psychiat. **39**:1213-1227 (June) 1938.

7. Notkin, J.; Coombs, H. C., and Pike, F. H.: Clinical and Experimental Observations on the Babinski Reversal, Cardiovascular Reactions, Respiratory and Pupillary Changes During the Convulsive and Post-Convulsive Stages of General and Experimental Epilepsy, Am. J. Psychiat. **11**:679-735, 1932.

8. Clark, S. L.: Responses Following Electrical Stimulation of the Cerebellar Cortex in the Normal Cat, J. Neurophysiol. **2**:19-35, 1939.

ments on them, and so they constitute the significant portion of the series for this study. With the animal under anesthesia induced with soluble pentobarbital U. S. P., electrodes were planted on the cerebral cortex. The cat was stimulated within twenty-four hours, or as soon as the anesthesia had sufficiently abated. The electrode consisted of a stainless steel tube with a tapering threaded end, containing in its axis a silver wire. The wire was fused into the middle of a glass rod, and this was encased in a rubber tube, all of which fitted tightly in the steel tube. The exposed tip of the silver wire embedded in the glass rod was ground flush with the glass, so that it would not injure the brain. The tube was screwed into a trephined hole in the skull far enough to touch the surface of the cerebrum through an opening in the dura. These plugs were allowed to remain for periods ranging from twenty-four hours to two months. From one to six plugs were placed on the cortex of each animal.

Through a detachable extension cord, electrical stimuli of controlled duration and voltage were applied to the cortex. The stimulating current was obtained from the 60 cycle, 110 volt lighting current, passed through a transformer and controlled by a rheostat. The usual duration of stimulation was two to four seconds, and the strength varied from 0.5 to 15 volts, as determined at the time of stimulation by a voltmeter across the leads to the cat.

Conditions of stimulation varied greatly, but usually a threshold response was obtained, requiring from three to five stimuli of low intensity, and then the voltage of a subsequent stimulus was doubled with the purpose of producing a seizure.

Detailed observations were taken on all stimulations, with as careful recording of movements during the seizure as possible.

RESULTS

Of the 62 cats which had convulsions in the course of experiments on them, 30 exhibited the unusual type of seizure to be described. We do not mean to place statistical value on these figures because the series is a select one. The slow seizures were produced by stimulation of many points on the exposed surface of the cerebrum (fig. 1). Other points not indicated in the figure include two on the gyrus cingulus, above the middle of the corpus callosum. The description of the seizure is best made by giving parts of three typical protocols.

Cat 1.—This animal gave a threshold response to a stimulus of 1 volt for two seconds from an electrode on the left motor area. The primary response was extension and protraction of the shoulder and elbow of the right foreleg. Three minutes after the last of seven stimuli at one minute intervals, a stimulus of 9 volts was applied for two seconds.

With the stimulus, there was immediate, strong clonic movement of the contralateral foreleg, followed by strong flexion of the contralateral hindleg. The animal then became quiet, holding a rather strained posture until about forty seconds after the stimulus, when the contralateral forepaw began to lift slowly and rhythmically. The head then turned slowly to the contralateral side and was followed in about ten seconds by replacement of the contralateral foreleg to the floor and slow lifting of the homolateral foreleg until the paw was over the head. For twenty seconds this leg was held thus and then lowered slowly to the floor. Ten seconds later both forelegs were lifted slowly and then gradually replaced,

with slow lifting persisting in the homolateral limb for twenty-five more seconds. The homolateral hindleg then began to lift slowly, the tail being turned in that direction. The cat would respond to stroking. Both hocks were then turned in and subsequently turned outward, with the animal walking in a "cake walk" fashion. Both the hindlegs lifted alternately and slowly, action dying out first in the homolateral leg but persisting in the contralateral one for thirty seconds longer. The tail was turned to the contralateral side while the contralateral hindleg was involved. The entire seizure lasted four minutes, and the cat cried frequently, in a gentle manner.

CAT 2.—This animal had two electrodes on the right frontal cortex; through the anterior one extension of the right forelimb at the elbow and shoulder was elicited with a threshold of 1.5 volts for two seconds. Three previous stimuli were given; then, after a ten minute lapse, a stimulus of 4.5 volts was applied for two seconds. With this stimulus there was strong flexion of the contralateral forelimb, followed by clonus of all four limbs. This persisted for about twelve

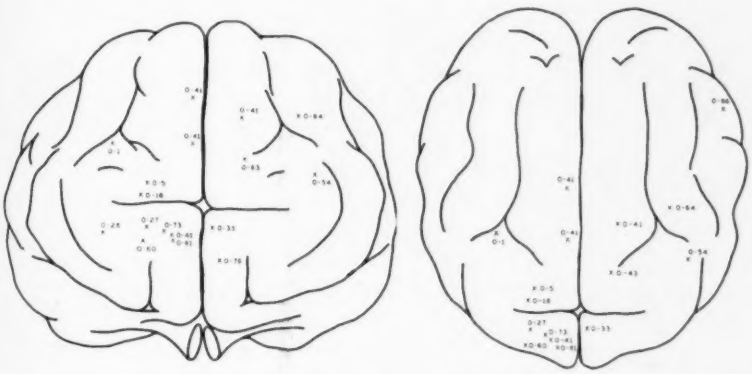

Fig. 1.—Two views of the cerebrum (anterior and dorsal) of the cat, showing the location of points from which slow seizures were elicited by stimulation through implanted electrodes. The cruciate sulcus is conspicuously shown crossing the median longitudinal fissure.

seconds; then the animal got to its feet and slowly lifted the contralateral forepaw. When this extremity was replaced, the contralateral hindleg began to lift slowly and rhythmically. This persisted for about twenty seconds and then ceased; the tail turned to the homolateral side, and after thirty seconds the homolateral hindleg began to lift in a slow manner. After forty seconds all activity ceased. A minute later slow, pleasure reactions appeared in the homolateral forepaw, the head being turned to the homolateral side. The pleasure reactions ceased, and the head turned to the contralateral side for a few seconds and finally returned to the midline. This seizure lasted about five minutes, but the placing reactions were not normal in any of the extremities for over eight minutes. Electrocorticograms were taken during the seizure, but were not conspicuously abnormal.

CAT 3.—This animal was stimulated through an electrode on the anterior end of the posterior suprasylvian gyrus on the right side. With the stimulus (6.7 volts for four seconds) there was immediate extension of the homolateral foreleg.

After thirty-five seconds the contralateral foreleg began to lift slowly, alternating with the homolateral extremity. The contralateral hindleg followed with similar slow lifting. The tail then turned to the homolateral side, followed by turning in and then turning out of the hocks and overstepping of both hindlegs. The homolateral hindleg then lifted slowly, and the cat tended to fall to that side. Twenty-five seconds later the homolateral foreleg lifted high over the homolateral ear. The entire seizure lasted about three minutes.

As seen from the protocols, the typical complete slow seizure occurred on stimulation of the cerebrum with a fairly strong stimulus (as judged by the threshold for elicitation of minimal activity). After such a stimulus, there was usually an immediate strong clonic seizure of short duration which involved strong flexion of the contralateral limbs. There was often associated pupillary dilatation. After a lapse of several

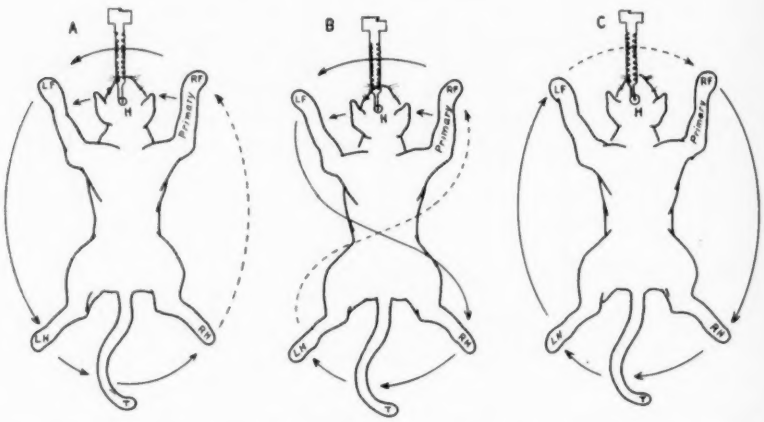

Fig. 2.—Three diagrams designed to show the sequence of involvement of the extremities, head and tail of the cat in the three complete patterns of slow seizures. In each case the stimulus is represented as being applied to the left motor area. The sequence of involvement following response of the primary forelimb is indicated by the solid lines, with arrow points. Dotted lines with arrows indicate the beginning of a possible repetition of the seizures. Similarity in shape of the solid lines with arrows in diagrams *A*, *B* and *C* to the letters *C*, *S* and *U*, respectively, explains the designation of these patterns in the text.

seconds the slow seizure commenced. The opening movement was a slow, deliberate, gentle lifting of the contralateral, "primary" extremity (i. e., a foreleg when the plug was on a "foreleg area"; fig. 3). From this point the sequence was open to some variation. Three general patterns were observed.

The most common sequence of involvement of the limbs we have designated as the C pattern (fig. 2 *A*). The contralateral forelimb was usually involved first; then the movement spread to the homolateral fore-

limb. These movements persisted for several seconds, and then the homolateral hindlimb began its slow movements; these in turn were followed by movements of the contralateral hindlimb. The action might then spread back to the primary limb and the entire process be repeated, but this was rare.

The pattern seen next in frequency was the S pattern, which, incidentally, was observed most commonly in the cerebellar seizures [8] (fig. 2*B*). After the slow lifting of the primary (contralateral) forelimb, the homolateral forelimb was involved in a similar lifting. The next limb to be affected was the contralateral hindleg, followed in sequence by the homolateral hindleg. The action might then start another circuit of the extremities, but, as with the C pattern, it usually died out after the first one was completed.

The third general sequence of involvement of the limbs was termed the U pattern (fig. 2*C*). After involvement of the primary forelimb, the next limb affected was the contralateral hindlimb, which was followed by the homolateral hindlimb and, in turn, by the homolateral forelimb. Again, but rarely, the circuit might be repeated wholly or in part without another stimulus.

The head and tail presented striking patterns of movement during these seizures, but they were not as constant as the movements of the extremities. During a seizure the head tended to turn in the direction of the hindlimb next to be involved. The head and the tail showed a definite tendency, after a turn to one side, to turn to the opposite side. The trunk reacted in a similar manner—strong concavity to one side was followed by strong concavity to the other. The movements of the head, tail and trunk were associated with each of these patterns of the slow seizure.

Throughout these slow seizures the animal appeared to be aware of its surroundings and was responsive to such stimuli as stroking or presenting of food. It seemed not to be especially disturbed by the uncontrolled gyrations of the extremities. An entire seizure varied in length from approximately two to fifteen minutes, but the average duration was about six minutes. After cessation of these movements, there were residual neurologic deficits, such as the loss of the placing reactions, in some animals. Attempts to elicit these were not made in all experiments.

The foregoing description is that of the complete slow seizure, by which is meant a seizure in which all four limbs, the head and the tail are involved. Only about one third of the seizures elicited were complete. Not all seizures exhibited by a single animal on successive trials were complete, but the general pattern of that part of the seizure which appeared remained the same.

Two movement patterns which are characteristic stages of complete seizures have been observed also to occur in and have been used to

identify the incomplete slow seizure. They are: (1) excessive pleasure reactions performed in a slow manner, and (2) high stepping movements of the hindlegs in which the hocks are turned in (fig. 3 *D*) and then turned out in a varus position, so that the animal "cake walks."

The pleasure reaction is the typical response of the animal to petting under normal circumstances and is the normal kitten's reaction while nursing. It is a dainty lifting of the paws, together with flexion of the toes and protrusion of the claws of the forefeet. It is executed rhythmically and alternately by the forelegs. In the slow seizure, it is first seen in the contralateral (primary) foreleg and then in the homolateral extremity, so that the two are involved simultaneously awhile, but the reaction tends to die out in the primary leg first. (In the complete type of slow seizure this response progressively changes to the high lifting movements.) During this type of response the animal frequently

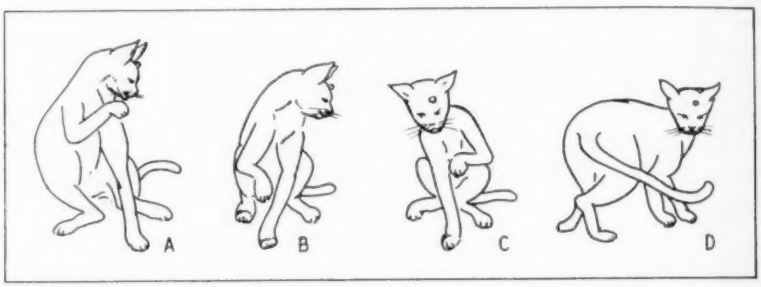

Fig. 3.—Sketches traced from portions of a moving picture of a cat taken during a slow seizure. The poses from *A* through *D* represent successive stages in the sequence of a seizure, such as that elicited from the left motor area.

purrs. The hock movements in the hindlimbs were seen in association with the pleasure reactions and were usually of longer duration.

It is difficult to define at just what point a slow seizure began and where it ended; however, in our observation, the occurrence of the pleasure reaction and the hock movements were considered to constitute the shortest possible slow seizure.

Certain operative procedures were carried out on some of these animals. In 2 cats bilateral ablation of the motor areas failed to affect either the slow seizure or the pattern thereof. In experiments designed to limit the spread of the neuronal discharge through cortical fibers by cutting through the cortex cerebri around the stimulated area, no alteration in the fit or the pattern was observed in 3 animals. In none of these was the cutting complete enough to isolate the point from the neighboring cortex. The slow seizure was not reproduced in 2 animals after removal of the cerebellum (though it had appeared from stimuli applied to the same electrode before removal of the structure), but it was

possible to produce a jacksonian type of seizure from the same point after its removal.

Section of one basis pedunculi in 1 animal was followed by a striking alteration in the sequence of limb movements, but made no difference in the type of movement. Prior to section of the basis pedunculi this animal showed a typical S pattern (fig. 2*B*). After the section, the response of the contralateral, primary limb was at first absent, the sequence continuing as before, with the primary limb involved last.

Section of the corpus callosum of 1 animal likewise did not abolish the type of seizure, but it was followed by alteration of the sequence of the limb movements. Prior to section of the corpus callosum, the pattern was of the C type; however, during a seizure after sectioning, slow movements of the contralateral foreleg did not appear, while the head and tail (midline structures) were involved to a much greater degree. The hindlegs were involved simultaneously after the head and tail had completed their movements.

COMMENT

Seizures of such similar character elicited from stimulation of the cerebrum or cerebellum suggest intimate relationships and bring to mind the occasional difficulty in distinguishing clinically between lesions of the frontal lobe of the cerebrum and those of the cerebellum. In the case of lesions of the two areas destruction of tissue and perhaps functional deficits are most conspicuous, in contrast to the present experiments, in which excitation of the two regions is involved primarily. It is of course possible that the effects observed here are also related to functional deficits, since the negative placing reactions may imply temporary abeyance of cortical function.

In the observation of the slow seizure, as elicited from the cerebral cortex of the cat, it has not been possible, to date, to determine the mechanism of spread and production or the exact localization. However, certain generalizations and inferences can be drawn.

The similarity of the slow seizures elicited from the cerebrum to those obtained from mechanical or electrical stimulation of the cerebellar cortex is so striking that for convenience we have come to term those elicited from regions other than the cerebellum "cerebelloid" seizures. While the origin of the seizures is obscure, some points suggest a definite cerebellar involvement: (1) the nature of the movements—slow, deliberate, graceful and identical in character with those produced after stimulation or production of small lesions of the cerebellar cortex; (2) the "rebound" phase of almost every movement—i. e., a movement of a limb is paired with a similar movement of the opposite one, and movements of the head, body and tail alternate in direction; (3) the extreme lability of the seizure to fatigue, drugs, etc., which is also true

of cerebellar seizures, and (4) the failure to reproduce the cerebelloid seizure in 2 animals (electrodes on the cerebral cortex) after removal of the cerebellum, although the rapid clonic seizure was elicited. In the light of the third point the fourth has less significance than might be indicated.

It appears likely that the cerebelloid seizures occur with much greater frequency than is suggested by the 30:62 ratio and that they are overshadowed by the less labile clonic convulsions. At times the clonic fits last for as long as several minutes after strong stimuli, and alterations in the posture (flexion or extension) of the clonically involved limbs are frequently slow and may represent the cerebelloid pattern with clonus superimposed. A careful analysis of slow motion moving pictures of cats during the clonic attacks would be important in demonstrating the presence or absence of a cerebelloid sequence. This possible interpretation is further supported by the fact that the end of a cerebelloid sequence is often the only obvious evidence of the cerebelloid attack after the clonic movements have ceased.

That visceral activity (except pupillary dilatation, which also accompanies true cerebellar seizures) apparently is absent in the cerebelloid attacks, although it is an important component of the clonic seizure, suggests that two projection systems are involved, either from the cortex (the point stimulated) or from some lower "level." Obviously, autonomic pathways are involved in the clonic attacks, and it appears likely that these are not completely of cortical origin, since large cortical ablations do not prevent their occurrence. It would be valuable to know whether the pupillary dilatation is the result of the activity of the dilator muscles or of the constrictor muscles (oculomotor inhibitions) of the iris, in view of Hodes and Magoun's [9] demonstration of the widespread origin of the latter and the relatively limited regions of origin of the former.

Certain predisposing factors may be involved in production of the cerebelloid seizure. It has been noted repeatedly that such a seizure was more frequently elicited from an animal of gentle disposition, and if the cat was angered or irritated, the seizures were often not elicited (inhibited or submerged). The similarity of certain phases of the cerebelloid seizure to normal actions and motions (though caricatured) of the cat is also striking, such as the pleasure reactions, the slow movements of the body and tail and, not infrequently, the associated purring.

The location of the stimulating electrode on the cortex may be a factor in the elicitation of the cerebelloid seizure; seizures have occurred, however, after stimulation of surface points both in and out of the "motor" area and on the gyrus cinguli, on the median surface of the brain. That cerebelloid seizures could be elicited after removal of the motor areas

9. Hodes, R., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Forebrain and Midbrain with Special Reference to the Pupil, J. Comp. Neurol. **76**:169-190, 1942.

or after section of one basis pedunculi indicates that integrity of the pyramidal tract is not essential for the slow type of seizure, a conclusion which also holds for the clonic fits (unpublished experiments; Ward and Clark [6]).

SUMMARY AND CONCLUSION

An unusual type of seizure following electrical stimulation of the cerebral cortex of the unanesthetized cat is described. The seizure is slow and strikingly similar to that elicited from the cerebellar cortex of the unanesthetized cat. Its mechanism is yet to be determined. It is a distinct entity, quite separate from the usual "jacksonian seizure" also elicited from the cerebral cortex.

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PARAPHENYLENEDIAMINE POISONING WITH CHANGES IN THE CENTRAL NERVOUS SYSTEM

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NEW YORK

The prevalent use by women of coal tar products as hair dyes, sold in the market under various trade names, is well known. "Ursol," a paraphenylenediamine coal tar chemical, is a popular preparation. When such a dye is used excessively, vertigo, gastritis, diplopia, asthenia and exfoliative dermatitis may result. Although neurologic complications, such as dizziness, nystagmus and tinnitus, have been recorded, histopathologic reports of involvement of the central nervous system were not found in the literature.

REPORT OF A CASE

L. M., a woman aged 51, was admitted to the Montefiore Hospital on Dec. 22, 1939 with a history that for about one and a half years she had been dyeing her hair with "ursol." In December 1938 she experienced pain in the knees. In June 1939 she noticed yellowish discoloration of the entire skin and the finger nails. In August 1939 she complained of dyspnea on exertion, occasional palpitation and loss of about 30 pounds (13.6 Kg.) in weight. During this interval there was low grade fever. In the early part of September 1939 there appeared tender blisters over the tongue, which slowly subsided. At this time the patient suffered from abdominal pain, pronounced anorexia and weakness.

General Examination.—There was a peculiar, yellow-grayish discoloration of the skin of the entire body and of the nails which matched the color of the dyed hair. The dorsum of the tongue was smooth. The heart was slightly enlarged to the left, and the second aortic sound was greater than the second pulmonic sound. There was some evidence of auricular fibrillation. The blood pressure was 110 systolic and 70 diastolic. The liver was 4 fingerbreadths and the spleen 3 fingerbreadths below the costal margin. Motion of the interpharyngeal joints was decreased.

Neurologic Examination.—There were deep muscle tenderness of both calves; slightly exaggerated reflexes, especially in the lower extremities; left ankle clonus; absence of abdominal reflexes, and a questionable Babinski sign bilaterally. No evidence of sensory changes was apparent. There was suggestive facial paralysis of supranuclear type.

From the Neuropathologic Laboratory and Neuropsychiatric Service of the Montefiore Hospital for Chronic Diseases.

This paper was read at a joint meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, and the New York Neurological Society on March 10, 1942. The discussion appeared in the October 1942 issue of the ARCHIVES, page 672.

Laboratory Data.—The urine contained albumin, 2 white cells per cubic millimeter and granular and hyaline casts. Examination of the blood disclosed 72 per cent hemoglobin, 3,600,000 red cells and 5,750 white cells, with 38 per cent polymorphonuclear leukocytes, 16 per cent metamyelocytes, 2 per cent myeloblasts, 27 per cent lymphocytes, 4 per cent mononuclears, 2 per cent eosinophils and 1 per cent basophils. The blood smear showed anisocytosis, macrocytosis, poikilocytosis and polychromatophilia.

Roentgen examination of the skeletal system revealed hypertrophic changes in the spine, hip joints, sacroiliac bones and bones of the lower extremities and hands.

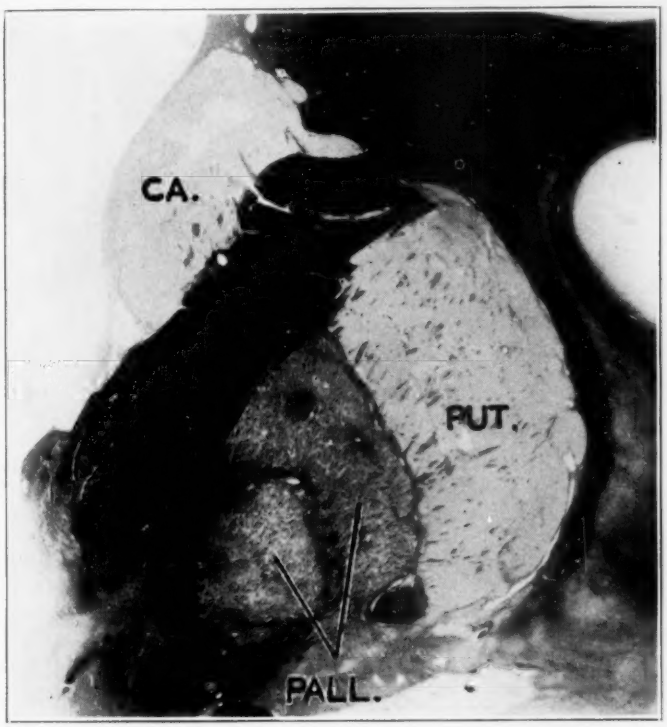

Fig. 1.—Pallor of the pallidal segment, thinning of the ansa lenticularis and slight status marmoratus of the putamen. Myelin sheath stain.

Course.—During her stay in the hospital the patient complained repeatedly of severe asthenia, anorexia and epigastric pain and appeared drowsy. She had a low grade fever, the temperature ranging from 99 to 100 F. and rising nightly to 102 F. She received all forms of vitamin therapy, which led to disappearance of the glossitis. The neurologic picture remained unchanged. The aforementioned symptoms became more severe, and for about two months before death the knee and ankle jerks were unobtainable and there were definite left ankle clonus and Babinski sign bilaterally. The anemia became more severe. She received several transfusions, but her condition gradually became worse, and she died on March 9, 1940.

General Pathologic Observations.—The skin was yellowish gray. Hepatosplenomegaly, ascites and atherosclerosis of the coronary arteries and aorta were observed on gross inspection. The liver was 4 fingerbreadths below the costal margin and weighed 2,500 Gm. The capsule had a glistening appearance, and the underlying tissue was moderately granular. The organ cut with increased resistance. Microscopically, there were atrophy of the hepatic cords, foci of necrosis of liver cells and occasional areas of proliferation of biliary ducts. The

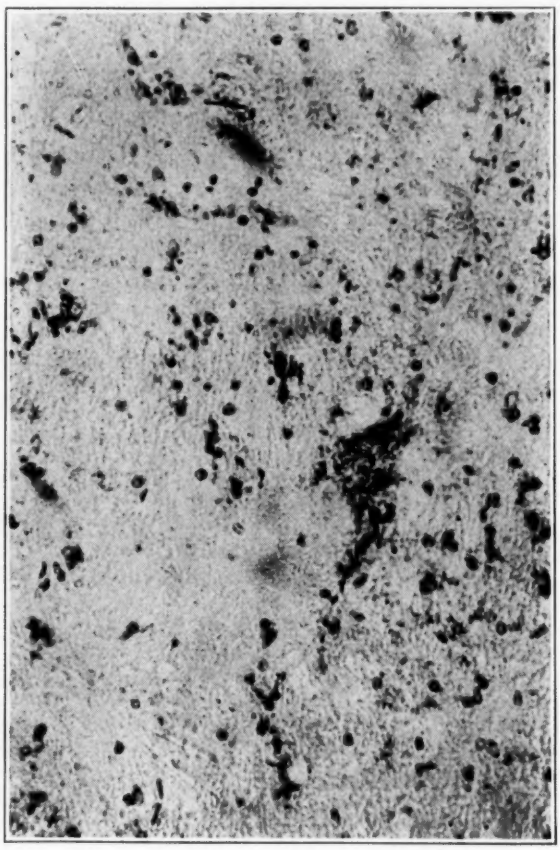

Fig. 2.—Pigmentary accumulations in pallidal segments. Turnbull blue stain; × 200.

spleen was tremendously enlarged, weighed 1,420 Gm. and was firm. There was an infarction in the upper pole. Microscopically, the follicles appeared indistinct, and the pulp was greatly congested. The area of infarction at the edge was fairly well demarcated from the adjacent splenic tissue by an extremely congested zone.

Brain and Spinal Cord.—Gross Examination: The dura, especially the under surface, had a yellowish tinge. The brain had a pronounced pallor and weighed

1,420 Gm. The pia-arachnoid stripped readily. No other abnormalities were noted. Except for pallor, the cord showed no abnormalities.

Microscopic Examination: Sections from various regions of the cortex, diencephalon, dentate nucleus, cerebellum, brain stem and spinal cord were stained for

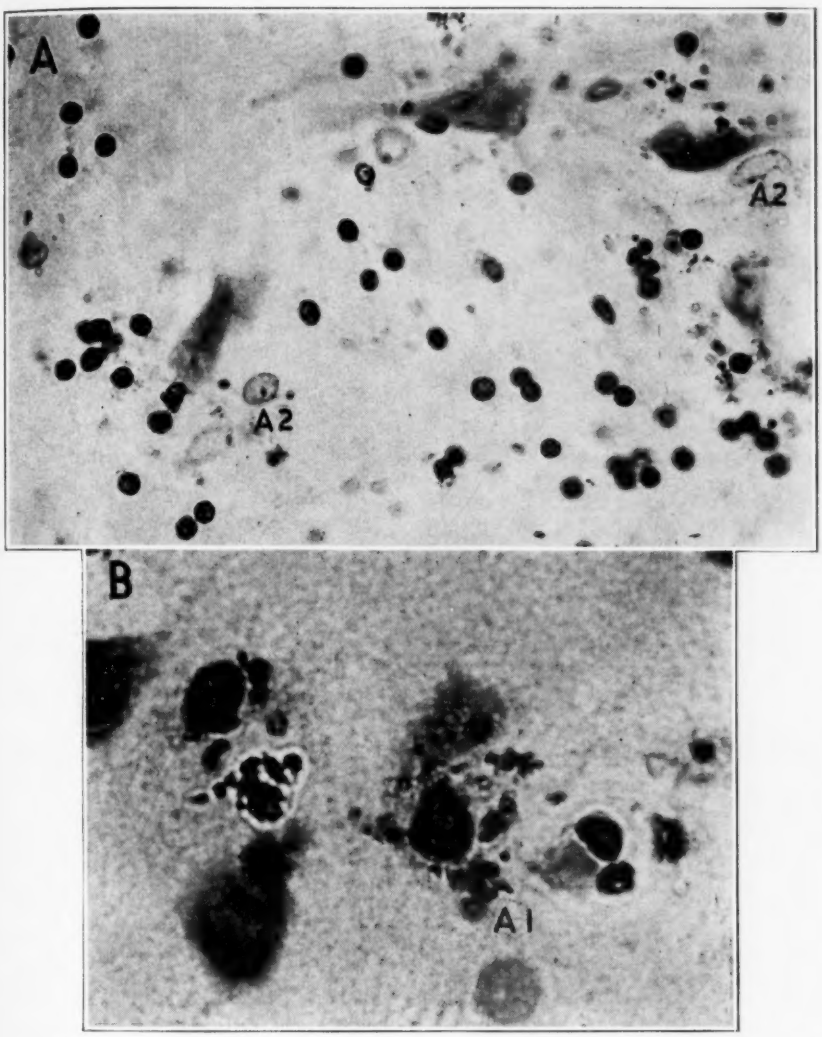

Fig. 3.—*A* (× 400), Alzheimer cells type II, with slight accumulation of pigment granules around them. Notice the diseased pallidal nerve cells. *B* (× 900), Alzheimer cells type I. Cresyl violet stain.

myelin sheaths and with cresyl violet. Some of the sections of the cortex and the basal ganglia were fixed in alcohol and stained with cresyl violet and with Turnbull blue. Frozen sections were also stained by the myelin sheath, Bielschowsky, sudan III and Holzer methods.

Cortex: Sections from various regions of the cortex disclosed a normal arrangement of the cytoarchitectural layers, with preservation of the nerve cells. An occasional nerve cell showed evidence of chromatolysis. There were also a few Alzheimer glia cells type II, surrounded by a slight amount of pigment.

In the hippocampus, in addition to the aforementioned changes, there were numerous accumulations of amyloid bodies. The slight changes in the ganglion

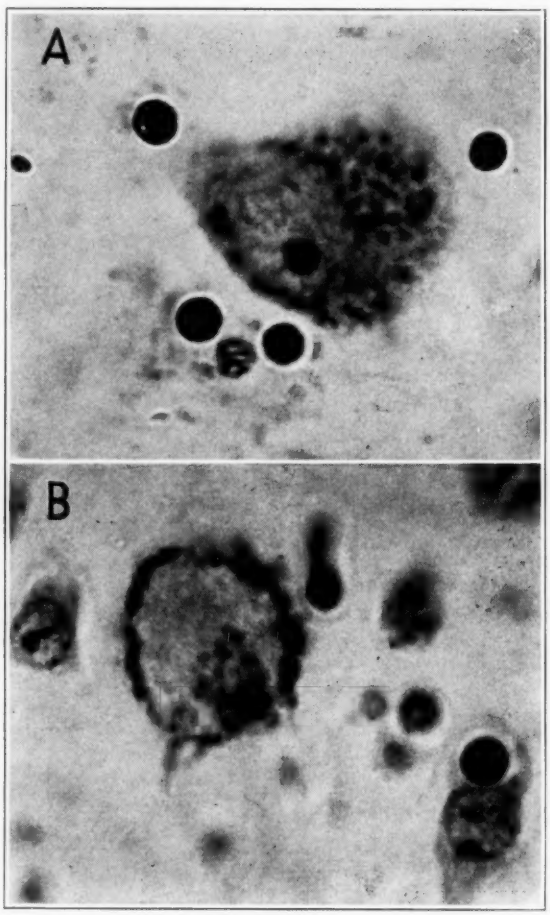

Fig. 4.—*A* (× 1,200), pigment accumulations in one of the nerve cells, with the nucleus displaced to the periphery. *B* (× 900), chromatolysis, accumulation of Nissl substance at the periphery and collections of pigment granules. Cresyl violet stain.

cells were more prominent in this than in the other cortical regions. Sommer's sector appeared normal.

Diencephalon: Sections were made of the basal ganglia through the rostral part of the pallidum. There was pronounced pallor of both pallidal segments (fig. 1), with almost complete disappearance of the ansa lenticularis. The putamen had a slight

marble-like appearance (fig. 1). With high power magnification the myelin sheaths of the pallidal fibers showed slight swelling and beading. An occasional swollen axis-cylinder was noted. In the Turnbull blue preparations the entire pallidum took a bluish stain. There were heavy deposits of bluish iron pigment throughout the pallidal segments (fig. 2), with numerous Alzheimer cells types

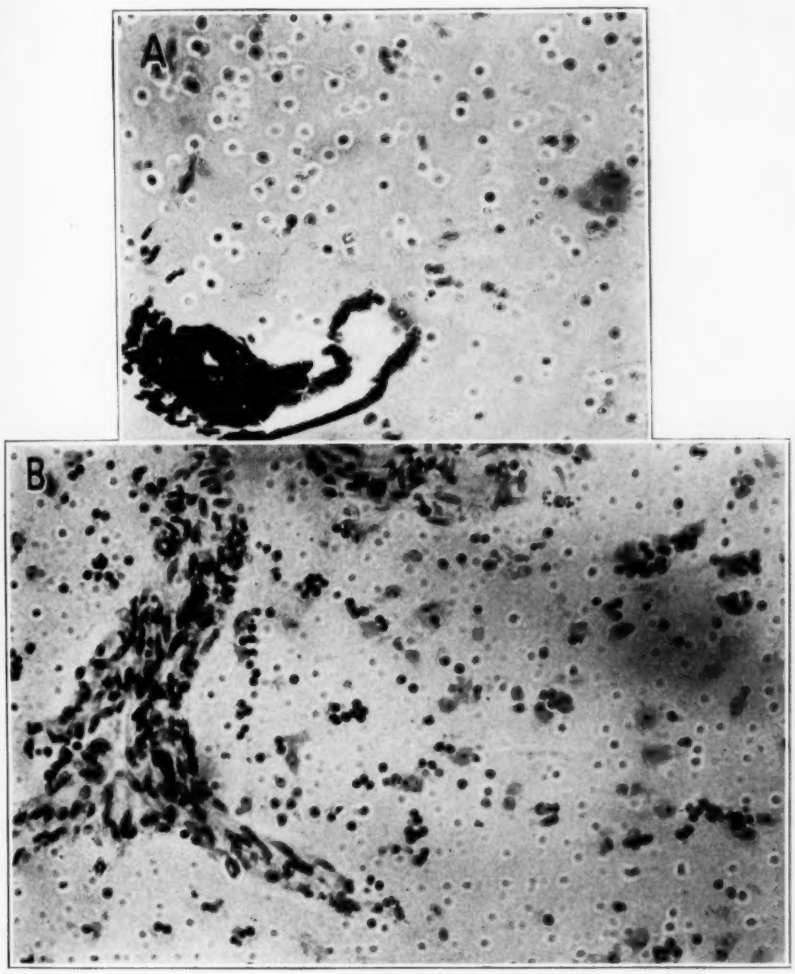

Fig. 5.—*A* (× 190), calcific and iron deposits around a vessel. Notice the pigmentary deposits in the pallidal nerve cell. *B* (× 190), proliferating vessels of the basal ganglia and increase in the glia nuclei. Cresyl violet stain.

I and II (fig. 3 *A* and *B*). Heavy deposits of bluish pigment were also observed in the walls of the vessels. The entire striatum took a pinkish stain, in contrast to the bluish stain of the pallidum. It contained fewer Alzheimer cells and less iron deposits than the pallidum. In the cresyl violet preparations the pallidal nerve cells were decreased in number; they appeared pale and showed marked

loss of chromatin material or were almost completely disintegrated (fig. 3 *A* and *B*). Many of the pallidal nerve cells contained heavy brown-bluish pigmentary deposits, which were usually situated at the periphery of the cell (fig. 4 *A*). In other cells the Nissl substance had collected at the periphery, and the pigment granules were usually situated at one of the poles of the cell (fig. 4 *B*). The pigmentary deposits were somewhat similar to the accumulations seen in cases of pigment atrophy. They differed somewhat from the latter in that they consisted

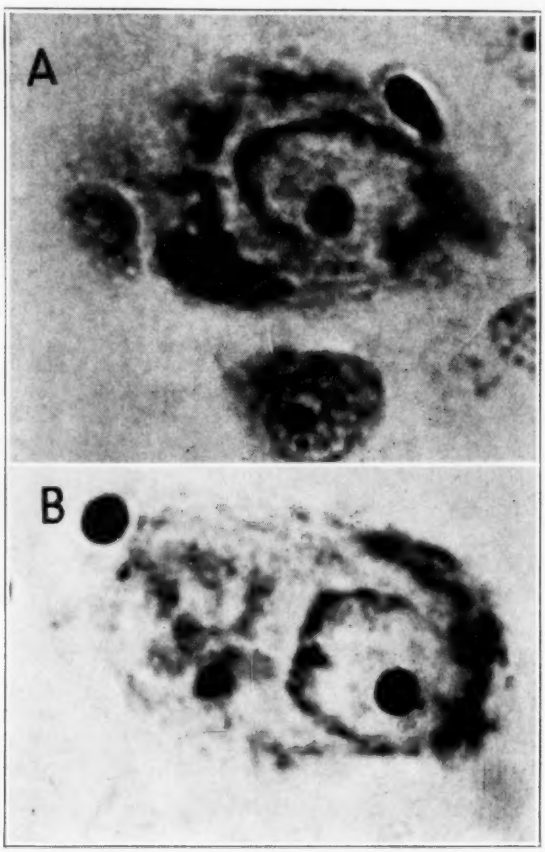

Fig. 6.—*A* (× 1,200), diseased nerve cell of the striatum, with some pigment accumulation and tendency of Nissl substance to accumulate at the periphery. *B* (× 1,200), severe disintegration of the nerve cell of the striatum. Cresyl violet stain.

of heavy granules (fig. 4 *A* and *B*). A number of the pallidal nerve cells were completely destroyed. They were recognized only by their nuclei and nucleoli, which, in turn, were surrounded by deposits of pigment (figs. 3 *A* and *B*). Some of the pallidal vessels were calcified (fig. 5 *A*), and others disclosed proliferation of the endothelial cells (fig. 5 *B*). In the striatum, the large nerve cells revealed changes somewhat similar to those of the pallidum, but less extensive. Some

showed chromatolysis, with a tendency for the Nissl granules to accumulate at the periphery of the nerve cell (fig. 6*A*), while others were severely diseased (fig. 6*B*). Sections through the middle of the striatum and pallidum disclosed changes similar to but far less extensive than those in the rostral portion of the pallidum. The nerve cells of the thalamic nuclei stained normally. There were no pigmentary deposits or Alzheimer cells.

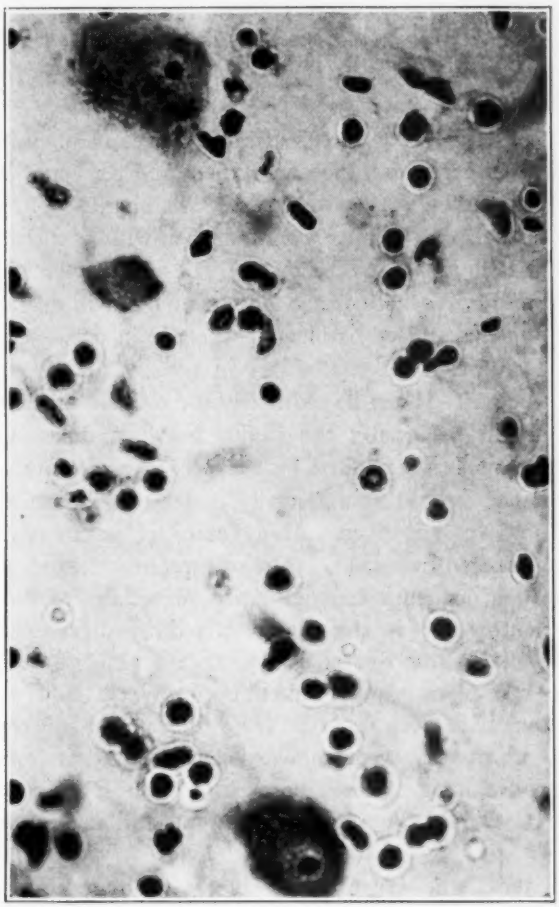

Fig. 7.—Nerve cells of the dentate nuclei with pigmentary deposits. Cresyl violet stain; × 400.

Hypothalamus: The lining of the third ventricle was slightly thickened. There were numerous deposits of amyloid bodies. The nerve cells of the hypothalamus showed some loss of their heavy iron pigment granules. In addition, many of the nerve cells, especially in the supraoptic nucleus, contained the same type of pigmentary deposit as did the nerve cells of the pallidum.

Cerebellum and brain stem: In the myelin sheath preparation the dentate nucleus showed no abnormalities. In the cresyl violet preparation there were

pigment atrophy of many of the nerve cells, ischemic cell changes, occasional chromatolysis and a few Alzheimer cells, surrounded by pigmentary deposits. Some of the nerve cells of the dentate nucleus showed the same heavy granular deposits as did the pallidal nerve cells (fig. 7). The nerve cells of the inferior olivary nuclei, except for pigment atrophy of the typical variety, were normal. The Purkinje cells appeared intact.

Spinal cord: No areas of demyelination were noted, but there were numerous amyloid bodies and the central canal was patent. A few of the anterior horn cells did not stain well, but did not present pathologic changes.

COMMENT

Most of the hair-dyeing agents are derivatives of phenylenediamine, There are several varieties: the ortho, meta and para and the dimethyl and diethyl derivatives. The paraphenylenediamine used by this patient is a dark or black crystalline, solid material with a melting point of 140 C. and a boiling point of 267 C. The dark color is due to the combination of the dye with iron. The compound is unstable, and on exposure it oxidizes and turns black, especially in an aqueous solution. It is difficult to purify. It crystallizes in benzine and is easily soluble in alcohol and ether. It can be oxidized by the blood and all the tissues of higher animals, especially the brain, heart, muscles, kidneys and liver. The reaction is facilitated by the presence of water.

The substance is used commercially under the name of "ursol" for dyeing furs and in hair dyes. Many cases of paraphenylenediamine poisoning have been reported. The symptoms elicited are vertigo, gastritis, diplopia, asthenia and dermatitis, especially of the exfoliative type. The acute onset is also characterized by dizziness, nystagmus and tinnitus. When the dye is used over a prolonged period gradual deafness may take place. Improvement occurs when the dye is removed. Some symptoms have been reported from the dye used in cosmetics and stockings. Asthma and eczema have been observed in workers using this dye in vulcanizing rubber industries, in fur-dyeing and feather-dyeing industries, in photographic developing and in textile dye intermediaries.

Experimentally, the dye produces in the rabbit edema of the head and neck. In addition, in rabbits and cats a rapid pulse and increased respiration, with wheezing and hypothermia, develop. Convulsive seizures have been reported to occur in some mammals. Asthma is due perhaps to the constricting action of the dye on the bronchiolar musculature. It acts like histamine in stimulating smooth muscle and increasing capillary permeability, and thus produces edema. The meta derivative, when used experimentally, causes hydrothorax, chemosis, exophthalmos and lacrimation.

As already stated, numerous cases have been reported clinically (Close,[1] Möllerström [2] and Nott [3]), and in some instances references have been made to neurologic signs and symptoms, but no cases with pathologic studies of the central nervous system have been described. In the cases in which necropsy was performed (Israëls and Susman [4] and Peters and Sachs [5]) the lesions observed were acute, subacute or focal necrosis of the liver, hepatosplenomegaly, severe congestion of the viscera and anemia. Israëls and Susman [4] mentioned that "the brain showed a definite acute congestion of the cortex and white matter throughout. The appearance was that of a toxic encephalitis." Apparently, microscopic examination had not been made. Peters and Sachs [5] reported clinically a case of impairment of proprioceptive sensation and apparent loss of vibratory sensation below the third lumbar vertebra. Unfortunately, the central nervous system in this instance was not obtained at autopsy. Neurologic complications were also mentioned by Close [1] and Keschner and Rosen.[6] In Close's [1] case nystagmus, tinnitus, giddiness and headaches were the outstanding neurologic symptoms. Keschner and Rosen [6] described a case in which the sole observation was papilledema and retinal hemorrhages. At first the possibility of an expanding intracranial lesion as the etiologic factor was considered, but careful investigation revealed that the patient was using a hair dye sold under the name of "Glo-Rnz." The following note appeared on the label of this product, as required by the federal Food, Drug and Cosmetic Act for all "coal tar hair dyes." [7]

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1. Close, W. J.: A Case of Poisoning from Hair Dye (Paraphenylenediamine), M. J. Australia **1**:53 (Jan. 9) 1932.

2. Möllerström, J.: Acute Intoxication from the Use of Aniline Dyes, Acta med. Scandinav. **71**:73, 1929.

3. Nott, H. W.: Systemic Poisoning by Hair Dye, Brit. M. J. **1**:421 (March 8) 1924.

4. Israëls, M. C. G., and Susman, W.: Systemic Poisoning by Phenylenediamine: Fatal Cases with Pathological Report, Lancet **1**:508 (March 10) 1934.

5. Peters, H. R., and Sachs, M. S.: Systemic Poisoning Due to Synthetic Organic Hair Dye: Fatal Case with Autopsy, Ann. Int. Med. **12**:2032 (June) 1939.

6. Keschner, M., and Rosen, V. H.: Optic Neuritis Caused by a Coal Tar Hair Dye, Arch. Ophth. **25**:1020 (June) 1941.

7. Federal Food, Drug and Cosmetic Act and General Regulations for Its Enforcement, Service and Regulatory Announcements, Food, Drug and Cosmetic, no. 1, Food and Drug Administration, United States Department of Agriculture, 1939, sect. 601 A.

This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to the accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Ocular disturbances are most likely the result of application of these dyes to the eyelashes and eyebrows. Toxic optic neuritis, as in Keschner and Rosen's [6] case, is an unusual complication of this type of poisoning. Berger [8] and Veasey [9] also reported cases of toxic optic neuritis in patients who used aniline dyes.

In the case reported by Keschner and Rosen,[6] a strong solution of ammonia was used to remove the dye from the forehead, and this may have been a factor in the toxic optic neuritis. Mackenna [10] and Israëls and Susman [4] expressed the belief that it is dangerous to attempt to remove the dye from hair with hydrogen peroxide or sodium thiosulfate, as use of these substances may intensify the symptoms. Baldridge [11] emphasized that application of heat and ammonia during the giving of a "permanent wave" may aid in the rapid absorption of the dye.

The outstanding neurologic signs in the case presented were asthenia, anorexia, drowsiness, muscle tenderness, slightly exaggerated deep reflexes, left ankle clonus, absence of abdominal reflexes and plantar responses.

The essential histopathologic changes in the central nervous system were observed in the pallidum, the striatum, the hypothalamus and, to a slight extent, in the dentate nucleus. These consisted essentially of peculiar granular deposits in the nerve cells, which were similar to those seen in the oxidase reaction. The other pathologic changes in the nerve cells, the deposits of iron pigment and the Alzheimer cells in the striatum and pallidum were similar to those observed in cases of severe disease of the liver. The pathologic picture in this case consisted, therefore, of primary and secondary changes as a result of the paraphenylenediamine poisoning. The chemical which circulated in the blood stream in this instance induced the oxidase reaction in the nerve cells and other tissues of the body. The heavy pigment granules and the proliferation of the smaller pallidal vessels, similar to what is seen in cases of lead poisoning, were undoubtedly due to the direct action of the toxin on the nerve cells and the blood vessels. The primary process in the liver caused the secondary changes in the central nervous system. The iron deposits, the Alzheimer cells and the chromatolytic changes in the nerve cells of the striatum and pallidum were most likely secondary to the involvement of the liver.

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CONCLUSION

A case of paraphenylenediamine poisoning following the use of a popular hair dye named "ursol" is reported. In addition to the typical clinical and pathologic changes following such an intoxication, neurologic signs and symptoms, with pathologic changes in the central nervous system, also developed. The most important of these changes was the oxidase reaction, resulting in deposits of pigment granules in the nerve cells of the pallidum, the striatum, the hypothalamus and the dentate nucleus.

TREATMENT OF SCHIZOPHRENIA

FOLLOW-UP RESULTS IN CASES OF INSULIN SHOCK THERAPY AND IN CONTROL CASES

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The purpose of this report is to compare the results of insulin shock therapy in a group of schizophrenic patients with the results of conservative treatment in a group of similar patients used as controls. The control group has been reported on previously.[1] The criteria for diagnosis and such factors as economic, occupational and educational levels and racial composition were the same in the two groups. Likewise, the selection of the patients for admission to the hospital was identical. Thus the groups were directly comparable, and the value of insulin shock therapy can therefore be estimated.

METHOD

Sixty-six patients suffering from schizophrenia, in whom the disease processes were typical, were treated by means of insulin shock. This procedure was made routine; it consisted, briefly, of giving the patient progressively larger amounts of insulin until the dose was sufficient to produce coma within two or three hours after injection. The patient was allowed to remain in coma from one-half to three hours. The depth of coma was determined by the absence of the corneal reflex. Each patient was subjected to thirty periods of coma at the rate of six per week. It was found that with successive treatments progressively smaller amounts of insulin were required to produce the same desired depth of coma. Therefore our criteria for treatment were depth and number of comas. After the series of treatments the patient was kept in the hospital from three to four weeks before discharge.

After the patient left the hospital his condition was evaluated clinically at six month intervals, the minimum final follow-up period being one year and the maximum four years. The clinical status of the patient was rated according to four categories: 1. Complete recovery. The patient had lost all psychotic symptoms and was able to adjust on or above his previous social level. 2. Social recovery. The patient continued to show minor defects which were not noted by his associates and was adjusting socially at approximately his former level. 3. Improve-

From the Iowa State Psychopathic Hospital, State University of Iowa College of Medicine.

1. Malamud, W., and Render, N.: Course and Prognosis in Schizophrenia, Am. J. Psychiat. **95**:1039-1055 (March) 1939.

ment. The patient continued to show defects but was able to live in the community, adjusting, however, at a lower level than previously. 4. No improvement. The patient continued to show psychotic manifestations of the same degree as when he was in the hospital or had deteriorated. A fifth classification included patients who had died.

MATERIAL

These 66 patients were free from other diseases, as determined by their physical and neurologic status and by ordinary laboratory procedures. Thirty-six were men, and 30 were women. The ages ranged from 14 to 44 years, the average being 25.1 years. The average length of stay in the hospital, including the period of treatment, was twelve weeks. The schizophrenic subtypes were represented as follows: simple, 4 patients; catatonic, 3 patients; hebephrenic, 21 patients; paranoid, 14 patients, and unclassified, 24 patients.

The control group contained 132 patients: 60 men and 72 women. The average age was 28.4 years; the age range, from 13 to 58 years. The average length of hospitalization was seven weeks. The representation of the subtypes was as follows: simple, 12 patients; catatonic, 6 patients; hebephrenic, 39 patients; paranoid, 24 patients, and unclassified, 51 patients. The original data of Malamud and Render [1] were reexamined to obtain a control group having a comparable follow-up period.

TABLE 1.—*Comparison of the Final Clinical Status of Schizophrenic Patients Treated with Insulin Shock and That of a Control Group Over the Same Follow-Up Period of One to Four Years*

Group	Number	Complete Recovery	Social Recovery	Complete and Social Recovery	Improvement	No Improvement	Improvement and No Improvement	Dead
Insulin-treated.....	66 (100%)	8 (12%)	15 (23%)	23 (35%)	8 (12%)	34 (52%)	42 (64%)	1 (1%)
Control.....	132 (100%)	28 (21%)	15 (11%)	43 (33%)	14 (11%)	71 (54%)	85 (64%)	4 (3%)

The insulin-treated and the control group were drawn from the same racial, economic and cultural population, as nearly all were natives of Iowa. The selection of patients for admission to the hospital was also the same for the two groups. In general, chronic deteriorated patients were not admitted. In this way our groups differed from the usual state hospital population. The diagnostic criteria were also uniform. It may be noted from the foregoing figures that the control group was twice as large as the insulin group, but the relative percentages of the schizophrenic subtypes in the two groups were about the same. The period of stay in the hospital of the insulin group averaged five weeks longer than that of the control group. This was due to the additional time consumed by the insulin treatment.

RESULTS

In table 1 is compared the final clinical status of the two groups of schizophrenic patients. The subsequent courses for these groups were over the same interval of one to four years. From this table it would appear that there are differences between the two groups in the categories of complete and social recovery, the control group being favored

in the category of complete recovery and the insulin-treated group in the category of social recovery. Since, however, it was difficult to estimate whether a patient was completely or socially recovered, these differences are probably not significant. A more meaningful comparison may be obtained by combining the categories of complete and social recovery and those of improvement and no improvement. The percentages for the first combination are 35 for the insulin-treated group and 33 for the control group. For the second combination the percentages are 64 for each group. It is evident, therefore, that insulin did not increase the rate of remission of the insulin-treated patients as compared with that for the group treated conservatively.

TABLE 2.—*Clinical Status at Various Follow-Up Periods of Patients Treated with Insulin*

Group	Time After Discharge	Number	Complete Recovery	Social Recovery	Complete and Social Recovery	Improvement	No Improvement	Improvement and No Improvement
Insulin.....	Discharge	66 (100%)	1 (1%)	12 (18%)	13 (19%)	19 (29%)	34 (52%)	53 (81%)
	6 mo.	66 (100%)	8 (12%)	12 (18%)	20 (30%)	17 (26%)	29 (44%)	46 (70%)
	1 yr.	65 (100%)	8 (12%)	11 (17%)	19 (29%)	14 (22%)	32 (49%)	46 (71%)
	2 yr.	45 (100%)	5 (11%)	10 (22%)	15 (33%)	5 (11%)	25 (56%)	30 (67%)
	3 yr.	16 (100%)	3 (19%)	4 (25%)	7 (44%)	1 (5%)	8 (50%)	9 (55%)
	4 yr.	9 (100%)	1 (11%)	1 (11%)	2 (22%)	2 (22%)	5 (56%)	7 (78%)
Control *.....	16-28 mo.	39 (100%)	12 (31%)	2 (5%)	14 (36%)	5 (13%)	20 (51%)	25 (64%)

* The figures for the control group for a follow-up period of sixteen to twenty-eight months are included for comparison.

In table 2 is presented the clinical status by categories of the insulin-treated patients at the time of discharge and at intervals of six months, one year, two years, three years and four years thereafter. The figures for the control group for the sixteen to twenty-eight month follow-up periods are included for comparison. From this table it seems clear that for the periods of six months, one year and two years the figures for the combined categories of complete and social recovery for the insulin group are similar to those for the control group which cover approximately the same length of time. This is also true for the combined categories of improvement and no improvement. The low percentage of 19 for the combined categories of complete and social recovery at the time of discharge contrasts with higher percentages

reported by other investigators.[2] This may be explained by the fact that our patients were discharged three to four weeks after insulin treatment had been discontinued rather than kept in the hospital until they had reached the peak of their improvement. For the three and four year follow-up periods, the numbers of patients, 16 and 9, respectively, were too small for accurate comparison. This table seems to indicate that the remission rate for the various intervals from six months on were relatively stable for the duration of our follow-up period.

However, this does not mean that any given patient stays at a constant level of improvement. A separate analysis of the course of each patient was made through the successive follow-up periods. Twenty-one, or 32 per cent, of the patients maintained a fairly constant course. The condition of 20 patients, or 30 per cent, improved from

TABLE 3.—*Final Clinical Status of Patients Treated with Insulin Shock and of a Control Group at Last Follow-Up Period of From One to Four Years in Terms of Type of Onset*

Group	Onset	Total	Complete and Social Recovery	Improvement and No Improvement	Dead
Insulin	Acute	31 (47%)	14 (45%)	17 (55%)	
	Gradual	35 (53%)	9 (26%)	25 (72%)	1 (2%)
Total		66 (100%)	23 (35%)	42 (64%)	1 (1%)
Control	Acute	31 (24%)	14 (45%)	17 (55%)	
	Gradual	101 (76%)	29 (29%)	68 (67%)	4 (4%)
Total		132 (100%)	43 (33%)	85 (64%)	4 (3%)

the time of discharge to the final status; 10 patients, or 15 per cent, became worse. Fifteen patients, or 23 per cent, showed a fluctuating course of remissions and exacerbations. Eight of these 15 patients had the same status at the last follow-up period as at the time of discharge; 3 had become worse, and 4 had improved. From this it is evident that the course of schizophrenia after insulin therapy is a variable one.

Table 3 presents the clinical status at the last follow-up period of from one to four years for both the insulin and the control group in terms of type of onset. By acute onset is meant the sudden appearance

2. (*a*) Bond, E. D.: Continued Follow-Up Results in Insulin Shock Therapy and in Control Cases, Am. J. Psychiat. **97**:1024-1028 (March) 1941. (*b*) The Treatment of Schizophrenia, Insulin Shock, Cardiazol and Sleep Treatment, Proceedings of the Eighty-Ninth Meeting of the Swiss Psychiatric Association at Münsingen, Berne, Switzerland, May 29-31, 1937, ibid. (supp.) **94**:1-354 (May) 1938. Katzenelbogen, S.: A Critical Appraisal of the "Shock Therapies" in the Major Psychoses: Insulin, Psychiatry **2**:493-505 (Nov.) 1939; **3**:211-228 (May) 1940. Jessner, L., and Ryan, V. G.: Shock Treatment in Psychiatry, New York, Grune & Stratton, Inc., 1941.

of the fully developed psychosis, and by gradual onset is meant an insidious development of the psychosis. In each group there were 31 patients with acute onset, of which 14 patients, or 45 per cent, made either a complete or a social recovery. Of the patients with a gradual onset in the insulin series there were 35, of which 9, or 26 per cent, made a complete or a social recovery. This number is compared with 101 patients in the control group, of whom 29, or 29 per cent, attained a similar status. This implies that patients with an acute onset do not have a more favorable outcome when treated with insulin than when treated by conservative measures.

Table 4 shows the relationship between the clinical status at the last follow-up period and the duration of the illness. For both groups, of those patients ill less than six months, 44 per cent made a complete or

TABLE 4.—*Final Clinical Status of Patients Treated with Insulin Shock and of a Control Group at Last Follow-Up Period of From One to Four Years in Terms of Length of Illness Before Treatment*

Group	Duration of Illness	Total Number	Complete and Social Recovery	Improvement and No Improvement	Dead
Insulin	6 months	34 (52%)	15 (44%)	19 (56%)	
	7-18 months	14 (21%)	3 (21%)	10 (72%)	1 (7%)
	19 months and over	18 (27%)	5 (28%)	13 (72%)	
	Total	66 (100%)	23 (35%)	42 (64%)	1 (1%)
Control	6 months	57 (43%)	25 (44%)	29 (51%)	3 (5%)
	7-18 months	26 (20%)	7 (27%)	19 (73%)	
	19 months and over	49 (37%)	11 (22%)	37 (76%)	1 (2%)
	Total	132 (100%)	43 (33%)	85 (64%)	4 (3%)

a social recovery. Of those ill longer than six months, the decrease in the percentage who recovered was approximately the same in the two groups. These figures do not support the statement sometimes made [2b] that early treatment of schizophrenia with insulin produces a higher rate of recovery than early treatment by other methods.

COMMENT

The data presented indicate that patients suffering from typical schizophrenia and treated by the insulin shock method as described did not have a better rate of recovery than those treated more conservatively.

The insulin shock technic employed differed from some of the methods used elsewhere.[2b] Rivers and Bond [3] contrasted two methods of insulin therapy—one similar to ours, in which the insulin was

3. Rivers, T. D., and Bond, E. D.: Follow-Up Results in Insulin Shock Therapy After One to Three Years, Am. J. Psychiat. **98**:382-384 (Nov.) 1941.

decreased after coma levels were reached, and one in which insulin was increased. They reported that the latter method gave better results. It may be that differences in insulin shock technic yield different rates of remission.

In the comparison of the insulin-treated and the control group, it should be pointed out that the study was not strictly one of a group of schizophrenic patients treated with insulin and a group not treated at all. The patients constituting the control group were treated [4] on the theory that they had problems and conflicts which they were unable to solve. These were considered important for their illnesses. An attempt was made to understand the development of their personalities, particularly the difficulties that they had encountered in their efforts at adjustment. With this knowledge, reconditioning and reeducation through the use of individualized socialization programs, on the one hand, and attempts to solve the conflicts by psychotherapy, on the other, were carried out. However, all the patients of the control group could not be subjected to this complete program, primarily owing to factors limiting their stay in the hospital: Eight, or 6 per cent, remained but two weeks; 31, or 24 per cent, three or four weeks; 37, or 29 per cent, five or six weeks; 20, or 15 per cent, seven or eight weeks; 16, or 12 per cent, nine to twelve weeks, and 20, or 15 per cent, more than three months. Some of these patients were transferred to state hospitals; none, however, received insulin shock therapy.

The similarity between the courses of the control and those of the insulin-treated patients suggests a common factor in the two methods of treatment. This factor may be that pressure toward socialization was being exerted constantly on the patients from several directions. The insulin shock treatment may be thought of as one method of exerting such pressure, especially through the attention the patient receives in experiencing the comas. Insulin shock, therefore, would not be considered a specific therapy for schizophrenia.

CONCLUSION

Sixty-six patients suffering from schizophrenia were given insulin shock therapy, and the results were compared with those for a group of 132 patients treated by conservative methods. Analysis of the subsequent courses for the two groups showed similar remission rates. Insulin shock therapy by the method described does not increase the remission rate of schizophrenia over that with more conservative methods of treatment.

Iowa State Psychopathic Hospital.

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STATISTICAL CONTROL STUDIES IN NEUROLOGY

I. THE BABINSKI SIGN

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We became interested in control studies in neurology while investigating the significance of objective signs in cases of head injury. It is evident that as a result of the medicolegal importance of many of these problems a great deal of emphasis is usually placed on objective signs. More weight is usually placed on a Babinski sign or an ocular muscle palsy than on the most intense subjective distress. We often wondered how many of these positive neurologic signs existed before the accident. The subject of the frequency of these signs in people who were not injured began to attract our attention. Considering the great number of injuries in large industrial organizations, it would be important to know the incidence of positive neurologic signs in control groups. Control groups do not necessarily imply normal people. In this study control groups refer to persons not under observation or treatment for head injuries or their sequelae.

We decided to determine, if possible, how scarred the population is from the neurologic standpoint. Old head injuries which were not considered serious, unrecognized complications of infectious childhood diseases, abortive forms of degenerative and heredofamilial diseases of the nervous system, mild cerebrovascular accidents with no gross paralyses are a few of the better known conditions which can cause a persistent Babinski sign without the person presenting complaints which would have called attention to the existence of these disorders. Older studies on the incidence of the Babinski sign are of little value because of the small number of cases usually investigated and because of various recent influences which, in our opinion, may tend to increase the incidence of the Babinski sign. One must recognize such factors as the increased frequency of virus diseases, the more widespread use of chemotherapy and spinal anesthesia and the notable rise in the number of industrial and traffic accidents, as well as the greater frequency of degenerative disease because of the increase in life expectancy.

Our data were gathered from three sources.

1. The first group consisted of 1,000 persons with head injuries seen in private practice. It is interesting to note the greater incidence

of males, 100 males to 63 females, which no doubt is due to the fact that the former are exposed to greater hazards, especially in the industrial fields.

2. The second series consisted of 2,500 patients admitted for general conditions to the wards of the Morrisania City Hospital. Patients with a condition suggesting a neurologic disease were excluded. The age curve for this series had a bell shape, indicating that we have probably taken a fair sample of the population. According to the fifteenth census of the population of the United States, 1930, the ratio of males to females in the County of the Bronx, New York city, was 100 to 100.6. In our series there were 100 males to 209 females. The greater proportion of females is accounted for to some degree by the large number of women with gynecologic conditions in the series. Negroes constitute 1.02 per cent of the population of the Bronx. In our series Negroes comprised 11.6 per cent of the patients examined. This large number is probably explained by the lower economic status of the race and the fact that the hospital is a city institution. The Chinese represented 0.023 per cent of the total non-Negro population in the Bronx. In our series the Chinese comprised 0.18 per cent of this population. Children below the age of 5 years were not included.

3. The third series, consisting of 704 inductees into the Army between the ages of 21 and 35, was a somewhat select group, since we did not see many who had been rejected by the local board physicians.

This paper is confined to a consideration of the Babinski sign. This sign was considered positive only when there was definite and constant extension of the large toe on plantar stimulation. The same stimulus was employed throughout to the outer part of the sole of the foot. Stimulation was adequate but not nocuous.

A positive Babinski sign was found in 4.3 per cent of the patients with head injuries and in 4.3 per cent of the hospital controls. The first 1,000 consecutive hospital controls showed an incidence of 4 per cent. There is no significant statistical difference between this 4 per cent and the 4.3 per cent of the group with head injuries. The actual difference between the two figures is less than three times the probable error. The relatively high incidence for the control group may be partly due to the large number of persons over 50 years of age. There were twice as many persons over 50 in the hospital control series as in the group with head injuries. The Babinski sign was nearly four times as frequent in persons over 50 as in those under 50 in the series of 2,500 control subjects. Syphilis played a small role in accounting for the Babinski sign. There was a slight difference in the incidence of positive serologic reactions of the blood between the 107 hospital patients with a positive Babinski sign and a similar number of patients of approximately the

same age distribution without a Babinski sign. There was no significant increase in the incidence of positive Babinski signs in those with positive serologic reactions.

Further confirmation of the theory that age is a factor was the observation that 1.15 per cent of the hospital controls between 21 and 35 years of age (781 cases) and 1.25 per cent of the 704 inductees had a positive Babinski sign. The closeness of the figures obtained is additional evidence that we were dealing with random samples.

The literature reveals few similar studies on large numbers of people. Schüler [1] found extension, notably of the big toe, in 8 per cent of normal men and in 4 per cent of normal women. Cohn [2] described extension of the great toe, with either flexion or extension of the other toes, in 20 per cent of the cases in a series. Neither of these investigators indicated the number of persons examined. Collier [3] examined 100 adults in the medical wards of a general hospital who were free from acute disease and presented no sign of any lesion of the nervous system. There was no dorsiextensor response in any instance. Walton and Paul [4] did not elicit the sign in a group of 100 adult patients who were not suffering from any nervous disorders and in a group of 100 students at a girls' school. Prince,[5] in examining presumably healthy men between 22 and 33 years of age for civil service tests, found that the sign occurred in 1 of 156 persons. Davidson [6] examined 161 adults; 151 had non-neurologic or orthopedic spinal conditions, and 10 were medical students. He stated that isolated extension of the big toe with fanning of the other toes does not occur in normal adults. Three per cent showed extension of the big toe, with extension of the little toes as well. Yakovlev and Farrell [7] found a Babinski sign in 1 of 168 college students in a camp for the Reserve Officers' Training Corps.

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In the tabulation are indicated various factors reported in the literature which can cause the appearance of a fleeting Babinski sign. There were 28 patients with heart failure in the hospital series who had a positive Babinski sign. None of the other exciting factors listed were present. These variables must be borne in mind in making such control studies.

Exciting Factor	Author
Exercise—14 mile (22.5 kilometer) march	Yakovlev and Farrell [7]
Stay in bed for months or years	Sehestedt [7a]
Freezing (crymotherapy)	Davis [8]
Sleep	Hawthorne [9]; Rosett [10]; Kleitman [11]
Cheyne-Stokes breathing during apnea	Tournay [12]; Monier-Vinard [13]
Cardiac insufficiency	Lhermitte and Dupont [14]; Gondet [15]
Jaundice; hepatitis	Rolleston [16]
Hypoglycemia (spontaneous)	Feinier, Soltz and Haun [17]
Hypoglycemia (overdose of insulin)	Andersen [18]
Hypoglycemia (induced in psychosis)	Heiman [19]; Hoch [20]
Opium	Walton and Paul [4]
Delayed chloroform, sulfonal (diethylsulfonedimethylmethane), coal gas (carbon monoxide) and other poisoning	Elliott and Walshe [21]
Scopolamine	Zador [22]; Rosenfeld [23]
Amytal	Thorner [24]
Barbiturates	Ironside [25]
Carbon disulfide	Lewy [27]
Gasoline intoxication	Machle [28]
Nitrous oxide asphyxia	Courville [29]
Lead	Abraham and Baird [30]
Strychnine	Babinski, quoted by Gondet [15]
Paraldehyde	Personal experience
Vertigo	Berggren [31]

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(Footnotes continued on next page)

SUMMARY

The incidence of the Babinski sign was studied in three groups of subjects: (*a*) 2,500 patients with non-neurologic conditions admitted to a general hospital; (*b*) 1,000 patients with head injuries, and (*c*) 704 inductees into the Army.

Four and three-tenths per cent of patients in the first and second group had a positive Babinski sign.

The Babinski sign was found in 1.15 per cent of the hospital control series, who were between the ages of 21 and 35 years, and in 1.27 per cent of the inductees, of the same age distribution.

In the hospital series the Babinski sign was nearly twice as frequent in persons over 50 as in those under 50 years of age.

Various factors which may produce a transitory Babinski sign are listed.

1882 Grand Concourse.

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Case Reports

ABERRANT THYROID TUMOR OF THE VERTEBRAE WITH COMPRESSION OF THE SPINAL CORD

Recovery After Operation and High Voltage Roentgen Therapy

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We report an unusual case of vertebral tumor composed of normal thyroid tissue, with secondary compression of the cord. We have been unable to find an exactly similar case reported in the literature. Of special interest is the fact that complete recovery was obtained after operation and high voltage roentgen therapy.

REPORT OF A CASE

History.—F. G., a 27 year old, married, Italian-born post office clerk, was first admitted to the neurologic service of Bellevue Hospital on Sept. 7, 1932, with the following complaints: (1) progressive weakness of the legs for the preceding five months, at first noticed as a feeling of heaviness while running; (2) involuntary jerkings of his legs for the previous four months, worse in the right leg; (3) subjective feelings of numbness and tightness for the previous three months, at first noted in the left knee but soon followed by similar sensations in the right knee, with gradual extension up the body to the level of the chest; (4) urinary disturbances of five months' duration, initially in the nature of retardation of flow, followed two months before admission by a "drawn feeling like electricity" in both legs while voiding; (5) loss of libido of one month's duration, with sensations during orgasm similar to those experienced while voiding, and (6) pain in the lower thoracic portion of the spine for the previous month.

The only significant events in his past history were tonsillectomy one year before admission and herniorrhaphy eight years previously.

Physical Examination.—The results of examination were without significance except for the neurologic signs. The cranial nerves were normal. Sensory examination revealed hypalgesia and hypesthesia below the fourth thoracic level and loss of position sense in the toes. There was no deep pain when the achilles tendons were squeezed. Vibration sense was lost in the legs, and the sacral region was spared. Both lower extremities were spastic, with marked weakness. There was ataxia in the heel to knee test; all the deep reflexes of the legs were hyperactive, with bilateral ankle clonus; the Babinski sign was present bilaterally, and the abdominal and cremasteric reflexes were absent. There was tenderness on pressure over the third dorsal spine.

Laboratory Data.—The blood count revealed 4,360,000 red blood cells per cubic millimeter, 80 per cent hemoglobin (100 per cent is equivalent to 14.5 Gm. per hundred cubic centimeters) and 10,500 white blood cells per cubic millimeter, the

From the Neurological and Neurosurgical Service (Second Medical Division, Cornell University Medical College), Bellevue Hospital; Dr. Foster Kennedy, Chief of Service.

smear and the differential count being normal. The nonprotein nitrogen of the blood measured 30 mg. per hundred cubic centimeters and the blood sugar 92 mg. A culture of the blood was sterile; the Wassermann reaction of the blood was negative, and the basal metabolic rate was plus 14.8 per cent.

Roentgenograms of the spine showed some erosion of the transverse processes of the third thoracic vertebra, with no evident involvement of the vertebral body. Fluoroscopic examination showed nothing abnormal.

Lumbar puncture revealed a clear, colorless spinal fluid; the initial pressure was 180 mm. of water, and there was a complete manometric block on jugular compression. The cell count of the spinal fluid was 6 lymphocytes per cubic millimeter; the Wassermann reaction was negative, and the colloidal gold curve was 0000000000.

Operation.—Laminectomy was performed on September 28. The spinous processes of the third to the fifth thoracic vertebrae inclusive were exposed, which revealed a soft tumor involving and partially destroying these processes as well as the laminas of the second and third thoracic vertebrae. The tumor was described as pink, with the consistency of bone marrow, infiltrating and very vascular, with a tendency to bleed profusely wherever it was touched. The dura was not opened.

Pathologic Report.—The specimen of tumor tissue removed at operation consisted of "apparently normal thyroid tissue, with high alveolar epithelium and no evidence of malignancy. It undoubtedly represented aberrant thyroid tissue."

Postoperative Treatment.—After operation the affected vertebrae were treated with high voltage roentgen therapy, with gradual improvement. Examination on Nov. 6, 1932 revealed slight increase in the strength of the legs and some diminution in the sensory disturbance. Delay in starting the urinary stream was no longer present. The patient was discharged from the hospital on Dec. 9, 1932, improved.

Subsequent Course.—In August 1933 the patient returned to the neurologic clinic complaining of recurrence of the weakness in his legs and mild paresthesias in both feet. Neurologic examination at this time revealed a sensory level up to the fourth thoracic segment, with weakness of the legs. Ankle clonus and the Babinski sign were elicited bilaterally. The abdominal reflexes were absent. In short, there was recurrence of the original signs and symptoms. The patient was therefore readmitted to the neurologic service on Sept. 28, 1933.

On admission, neurologic examination revealed the same changes as those noted in September 1932, on his first admission. Lumbar puncture was again performed; the fluid was clear and colorless, with a partial manometric block and a total protein content of 100 mg. per hundred cubic centimeters. Neurosurgical consultation was requested, and operation was pronounced inadvisable. He was therefore given another course of high voltage roentgen treatments and discharged on Nov. 16, 1933, unimproved.

On Jan. 4, 1934 the patient was readmitted for the third time, complaining of a progressive downhill course since his previous admission. He had become more paralyzed and was bedridden. There was difficulty in starting the urinary stream. No symptoms of goiter or hyperthyroidism were observed on this or any other examination. The neurologic findings were again essentially similar to those on his original admission except that the paraplegia had become gradually more severe. Radiation therapy was again resorted to. Over the next few months no noticeable improvement occurred, and the patient remained bedridden.

The entire case was reviewed, and the absence of improvement, with the persistence of manometric block, seemed to warrant surgical reexploration. On May 17, 1934 laminectomy was therefore again performed. The previous scar was excised; the fascia and muscles were split, and the tumor was exposed.

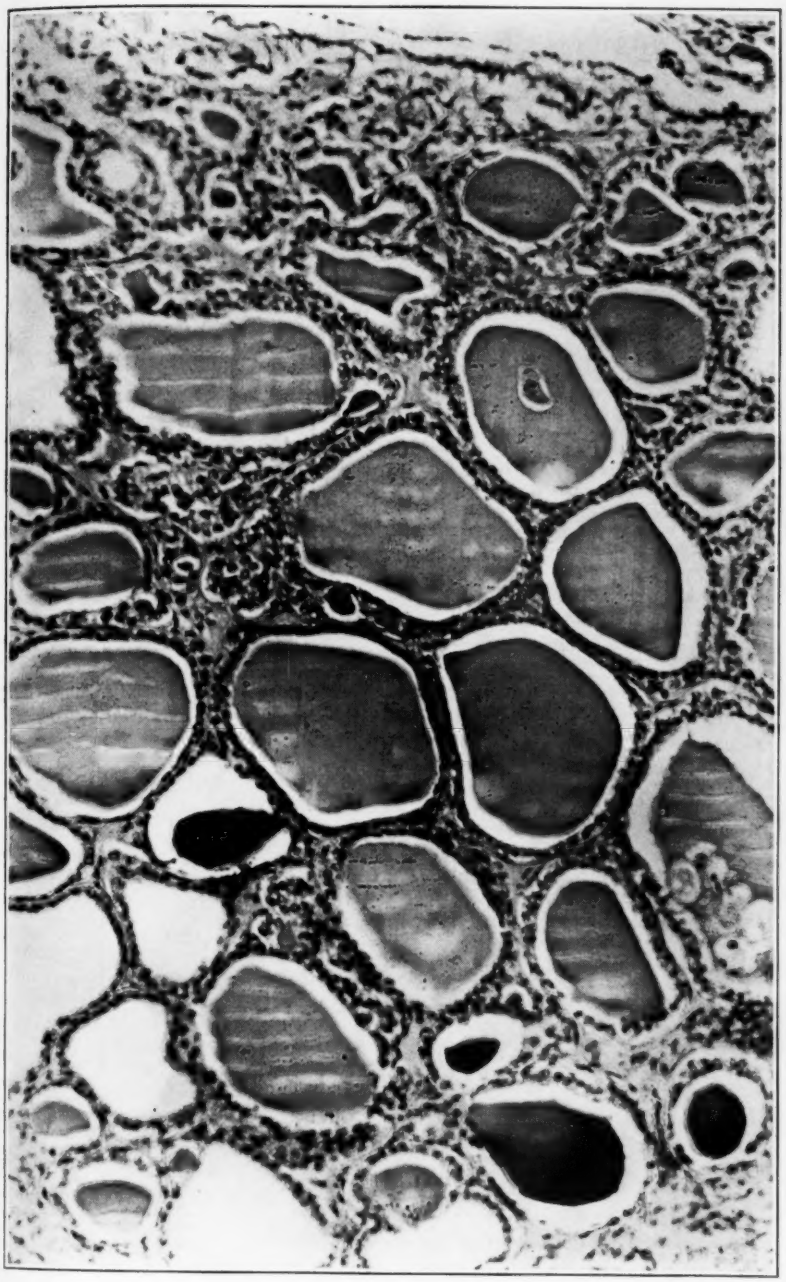

Fig. 1.—Portion of tumor tissue; × 192.

The growth was composed of reddish brown, soft tissue resembling normal thyroid in consistency and appearance. A large portion was removed with the curet. Because the tumor tissue had extended into the body of the fifth thoracic

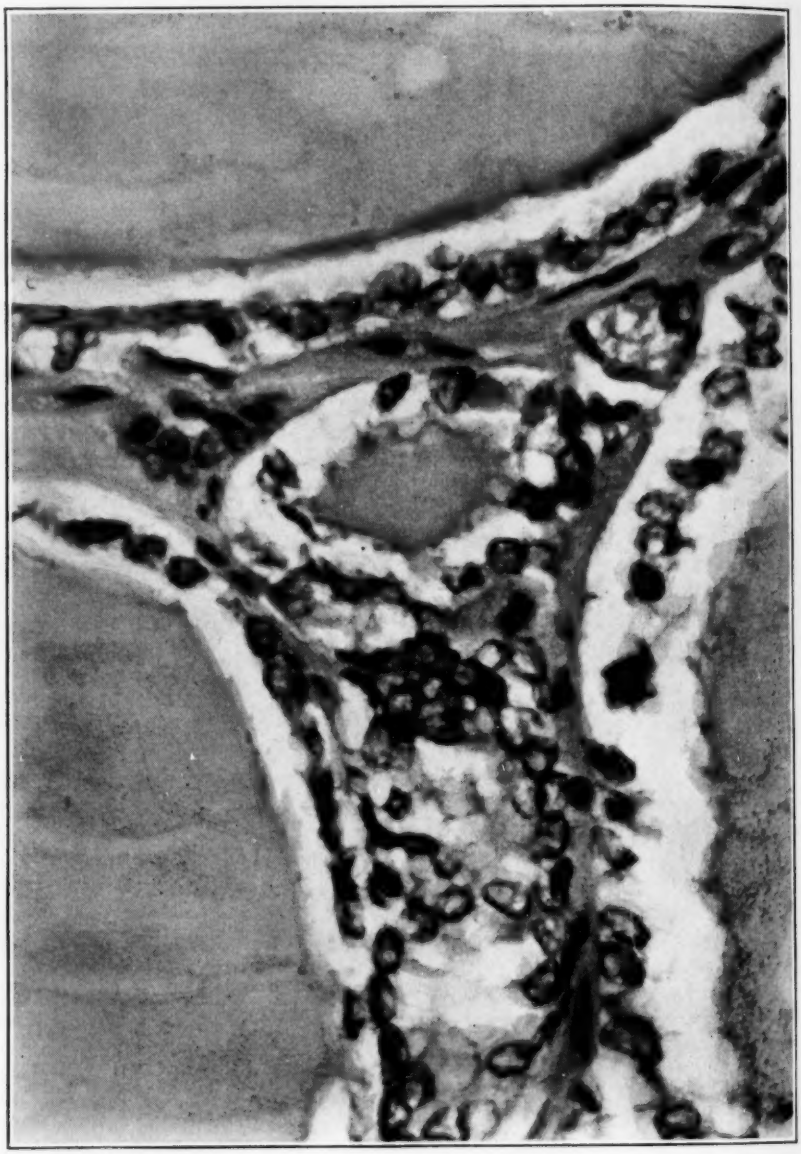

Fig. 2.—Higher magnification of a portion of the tumor tissue shown in figure 1; × 736.

vertebra, total removal was considered inadvisable. Pathologic study of this specimen of tumor revealed well preserved, normal thyroid tissue, which was not malignant.

After the second operation high voltage roentgen therapy was again instituted and continued over the next six months. Gradual improvement in the clinical

status occurred. At the time of discharge, in December 1934, the patient was able to walk and void normally, and only minimal sensory changes remained.

Since then he has been observed periodically and has had repeated neurologic examinations. At present, in January 1943, he has no subjective complaints; the neurologic status is normal, and the patient has been back at his usual employment as a post office clerk for the past eight years.

COMMENT

We believe that this case is unique in that (1) complete recovery has been obtained and the patient has been entirely well without further therapy for nine years, and (2) no tumor of the thyroid gland or any symptom of hyperthyroidism has ever been observed in this case. In view of the long period of observation (ten years), as well as the absence of signs of malignancy in the histologic sections of the tumor itself, one can rule out a metastatic carcinoma from the thyroid gland. It is therefore necessary in this case to assume that the spinal tumor originated either from aberrant thyroid tissue or from dislodged cells of normal thyroid tissue, the so-called benign thyroid metastasis. The latter condition of benign metastasis is one of extremely difficult definition. Ewing,[1] in discussing thyroid metastasis to the spine, pointed out that the tumor reproduces thyroid tissue with fidelity but that in most recorded cases, though the thyroid tissue itself is considered benign, the secondary deposits usually become malignant. This obviously did not occur in our case, possibly owing to the beneficial effects of the high voltage roentgen therapy. It should be recalled that the entire tumor mass was not removed surgically because of the extensive involvement of bone. No additional roentgen therapy has been administered since December 1934; yet no evidence of recurrence locally or in any other organ of the body has been noted. It therefore seems most logical to ascribe the lesion in our case to hyperplasia of aberrant thyroid tissue.

SUMMARY AND CONCLUSIONS

A case of aberrant thyroid tumor of the vertebrae with compression of the spinal cord and complete recovery following operation and high voltage roentgen therapy is reported.

The possible histogenesis is discussed.

The beneficial effect of high voltage roentgen therapy on such a lesion is stressed.

It is reasonable to assume, from the ten years of follow-up observation, that complete recovery has occurred.

No similar case of aberrant or benign metastatic thyroid lesion of the spine with complete recovery has been found in a review of the literature.

140 East Fifty-Fourth Street.

1. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1940.

News and Comment

COMMITTEE ON WAR PSYCHIATRY OF THE AMERICAN PSYCHIATRIC ASSOCIATION

The Committee on War Psychiatry of the American Psychiatric Association has published a study dealing with the steps which have been taken for the maintenance and improvement of civilian mental health in various types of communities throughout the country. The procedures used in state-wide areas, large cities and metropolitan districts and in small towns and rural areas have been assembled, and their fundamental principles have been described.

This publication may be obtained without cost on application. More detailed information on particular aspects of civilian mental health may be secured on request. Such material for rural areas may be obtained from Dr. T. Raphael, University of Michigan, Ann Arbor, Mich.; for state-wide areas from Dr. F. H. Sleeper, 100 Nashua Street, Boston, and for large cities and metropolitan areas from Dr. D. Ewen Cameron, Albany Hospital, Albany, N. Y.

TOPEKA INSTITUTE FOR PSYCHOANALYSIS

The Topeka Institute for Psychoanalysis, which has since 1938 acted as a branch of the Chicago Institute for Psychoanalysis, has been authorized to function as an independent institute by the American Psychoanalytic Association and its constituent societies.

The aim of the Topeka Institute is primarily the training of physicians in the theory and practice of psychoanalysis; secondarily it aims to promote an adequate knowledge of psychoanalysis among members of professions with problems related to psychoanalysis, such as general medical men, psychiatric nurses, social workers and teachers.

In its curriculum for physicians the institute intends to provide, in addition to preparatory analyses, a complete program of psychoanalytic instruction covering all requirements laid down in the "Minimal Standards for the Training of Physicians in Psychoanalysis" of the American Psychoanalytic Association. In order to fulfil this, a three year period of theoretic instruction is regarded as necessary.

The institute will operate in three places: Topeka, Kan.; Los Angeles, and San Francisco.

AMERICAN BOARD OF NEUROLOGICAL SURGERY

The next examination of the American Board of Neurological Surgery will be held in Chicago, at the Illinois Neuropsychiatric Institute, on Feb. 15 and 16, 1943.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

STRUCTURES OF THE NEUROHYPOPHYSIS WITH SPECIAL REFERENCE TO NERVE ENDINGS. E. VAZQUEZ-LOPEZ, BRAIN **65**:1, 1942.

This investigation deals with the manner in which nerve fibers end in the hypophysis. It was made chiefly on frozen sections of the pituitary gland of the horse, some studies also being made on the ox, sheep, rabbit, guinea pig and rat. Nerve fibers were stained by silver and gold impregnation methods, various technics being followed in order to assure proper differentiation of connective tissue, nerve fibers and neuroglial prolongations.

Nerve fibers to the hypophysis arise in hypothalamic nuclei, pass through the eminentia media of the tuber cinereum and enter the stalk grouped together in thick, close-set bundles. As they enter the pars nervosa, they fan out, and toward the distal portion they form a dense network of fibers running in all directions. Many of these fibers end in the perivascular spaces formed by the neuroglia around the blood vessels of the neurohypophysis. In this acellular area, the nerve fibers are seen to form extensive arborizations, including various swellings, clubbings and meniscuses. This typical nerve ending apparatus in relation to the blood vessels is present in a profusion such as is rarely equaled elsewhere in the body.

A second group of fibers enters the pars intermedia, where it appears to come into direct contact with the epithelial cells of the region and to form expansions and other structures, suggesting that the nerve fibers end among these cells. Actual pericellular plexuses were not observed. A third group of fibers, in the most distal portion of the gland, forms a system of nerve bundles lying beneath the connective tissue capsule of the pars nervosa and ends in relation to special meningeal corpuscles which lie embedded in the thick fibrous covering of the apical region.

The nerve fibers and nerve endings innervating the meningeal corpuscles are similar morphologically to those ending in the perivascular networks, suggesting a similar function. The meningeal corpuscles appear to have only a sensory function. Furthermore, the morphologic appearance of the nerve endings in the perivascular spaces suggests a close relationship to perivascular nerve endings of a sensory character present in other parts of the body. These facts indicate that the great mass of the neurohypophysis consists of sensory elements and that the main function of the organ must be that of a gigantic perivascular receptive apparatus. Vazquez-Lopez suggests that this sensory system may consist of chemoreceptors and pressoreceptors concerned with regulation of metabolic and hormonal functions. This regulation is mediated through the diencephalic centers in which the nerve fibers to the neurohypophysis originate.

MASLAND, Philadelphia.

THE PRESENCE AND LOCALIZATION OF VITAMIN C IN THE CENTRAL NERVOUS SYSTEM. G. WOLF-HEIDEGGER, Confinia neurol. **4**:121, 1942.

The author studied the presence and localization of vitamin C in the brains of rats and of normal and scorbutic guinea pigs by the use of the histochemical method of Giroud-Leblond. By this method the silver granules indicating the presence of ascorbic acid could be seen in the various types of nerve cells in all the regions of the brains of rats and normal guinea pigs. These granules were noted only in the cell plasma, never in the nuclei. In the pyramidal cells the granules were present in the cone of origin and in the proximal portion of the

axon. Microglia and oligodendroglia showed a definite vitamin C reaction. No evidence of vitamin C was observed in the cells of the choroid plexus. The ependymal cells were free from granules. The peripheral nerves gave no vitamin C reaction. In scorbutic guinea pigs none of the investigated portions of the nervous system showed a positive reaction for vitamin C. DEJONG, Ann Arbor, Mich.

Physiology and Biochemistry

THE NORMAL RATE OF REDUCTION OF METHEMOGLOBIN IN DOGS. WILLIAM W. COX and WILLIAM B. WENDEL, J. Biol. Chem. **143**:331, 1942.

Methemoglobin contained within circulating erythrocytes of dogs is reduced to hemoglobin at a constant average rate of 11.3 per cent of the total pigment per hour. This rate, therefore, represents the maximum resistance of this species to accumulation of methemoglobin. Reduction of intracorpuscular methemoglobin is solely a function of enzyme systems contained within the erythrocytes. Ability to reduce methemoglobin is impaired by low body temperature. It is not affected by severe hypoglycemia or by blood sugar concentrations several times the normal. Capacity to convert methemoglobin to hemoglobin is not diminished even after all the blood pigment has been converted to methemoglobin four times in a relatively short period. PAGE, Indianapolis.

THE IN VITRO FORMATION OF PHOSPHOLIPID BY BRAIN AND NERVE WITH RADIOACTIVE PHOSPHORUS AS INDICATOR. B. A. FRIES, H. SCHACHNER and I. L. CHAIKOFF, J. Biol. Chem. **144**:59, 1942.

In vivo experiments with radioactive phosphorus have clearly established that liver and small intestine are organs in which phosphatide metabolism is great, while in brain it is low. The question arises whether nerve tissue can synthesize phosphatide or must acquire it from plasma. The authors have demonstrated that excised brain of young and old rats and nerve of dog form phosphatide in vitro. Slices as well as homogenate form it. PAGE, Indianapolis.

THE BEHAVIOR OF LIPIDS DURING AUTOLYSIS OF LIVER AND BRAIN. W. M. SPERRY, F. C. BRAND and W. M. COPENHAVER, J. Biol. Chem. **144**:297, 1942.

Neither cholesterol nor phosphatides change in brain or liver when autolysis occurs. They become concentrated because of the large loss of tissue during autolysis. Cholesterol is similarly concentrated in liver left free in the abdominal cavity. PAGE, Indianapolis.

ARTERIAL AND CEREBRAL VENOUS BLOOD: ARTERIAL-VENOUS DIFFERENCES IN MAN. E. L. GIBBS, W. G. LENNOX, L. F. NIMS and F. A. GIBBS, J. Biol. Chem. **144**:325, 1942.

The determinations of oxygen, carbon dioxide, p_H, lactic acid, sugar, total base and inorganic phosphorus have been measured on the arterial and the internal jugular venous blood of 50 intelligent, healthy young men with normal electroencephalograms. Samples of blood from an artery and the internal jugular vein were drawn simultaneously, thus permitting estimation of the metabolic activity of the brain. These data furnish normal control data for future studies of the metabolism of brains which are functioning abnormally. The respiratory quotient of the brain in this series was 0.99. This figure, together with data on the concentrations of sugar, lactic acid and oxygen in the blood entering and leaving the brain, indicates that sugar is the principal source of energy for the brain in vivo. However, not all the sugar is completely oxidized, for a small part appears to be converted into lactic acid. PAGE, Indianapolis.

A Study of the Nitrogenous Constituents of Tissue Phosphatides. E. Chargaff, M. Ziff and D. Rittenberg, J. Biol. Chem. **144**:343, 1942.

The distribution of ethanolamine and choline in partially purified phosphatides from liver, brain and heart was determined by the method of isotope dilution with N^{15}. The amino acid content of these phosphatides, as well as of samples from lung and egg yolk, was likewise determined. In a preparation of pig liver phosphatides 35.6 per cent of the amino nitrogen could not be characterized either as ethanolamine or as amino acid. All of the nonamino nitrogen in a hydrolyzate of this phosphatide was found to be present as choline. In a preparation of beef brain phosphatides all the amino nitrogen could be identified as ethanolamine and amino acid, whereas only 50 per cent of the nonamino nitrogen was accounted for as choline. In a preparation of pig heart phosphatides 86.8 per cent of the amino nitrogen was accounted for as ethanolamine and amino acid, and only 49.3 per cent of the nonamino nitrogen could be characterized as choline. The phosphatides from brain and lung were found to have the highest amino acid content. The egg yolk phosphatides were free of amino acid. Data on the effect of storage on phospholipid composition and a discussion of some of the implications of the experimental results are included.

Page, Indianapolis.

Cure of Paralysis in Rats with Biotin Concentrates and Crystalline Biotin. E. Nielsen and C. A. Elvehjem, J. Biol. Chem. **144**:405, 1942.

In a previous paper Nielsen and Elvehjem showed that a "spectacle eye condition" in rats, produced by the addition of 10 per cent egg white to a purified ration containing synthetic B complex vitamins, could be prevented and cured by the addition of biotin. If the rats were continued on the egg white ration for six to eight weeks after the "spectacle eye" symptom appeared, typical paralysis or spasticity of the hindlegs developed. The administration of biotin concentrates or biotin is specific for this syndrome. High levels of fat in the diet slightly prolong the onset of paralysis. Riboflavin, pyridoxine or the combination of the two vitamins was without effect. High creatine levels were observed in the leg muscles of paralytic rats.

Page, Indianapolis.

Occurrence of Sphingomyelin in Tissues of the Cat. F. E. Hunter, J. Biol. Chem. **144**:439, 1942.

Although the presence in tissues of at least three different phospholipids has been known for many years, the methods available limited earlier studies chiefly to the total phospholipid fraction in various tissues. Only in recent years have detailed studies concerning the lecithins and cephalins appeared and added to knowledge of their possible functions. Considerably less is known concerning the phospholipid sphingomyelin. The sphingomyelin concentration found in eleven tissues from cats varied from 0.075 per cent, in skeletal muscle, to 1.25 per cent, in the brain. The proportion of sphingomyelin in the total phospholipid ranged from 7.5 to 33.2 per cent, so that there was no correlation between sphingomyelin and total phospholipid. The values are compared with those found for tissues from other species by previous workers. Some possible relation of sphingomyelin to fat metabolism and special properties or functions of tissues are discussed.

Page, Indianapolis.

The Pyramidal Tract: The Effect of Pre- and Postcentral Cortical Lesions on the Fiber Components of the Pyramids in Monkey. A. M. Lassek, J. Nerv. & Ment. Dis. **95**:721 (June) 1942.

Lassek believes that there is no convincing proof that destruction of area 4 causes complete degeneration of the axis-cylinders within the pyramids of the medulla oblongata in primates or in other mammals. In this investigation he studied the effect on the fiber components of the pyramids of extirpations of the

precentral and postcentral cortex, using a refined silver stain as a criterion of fiber loss.

The left cerebral cortex in each of 6 monkeys was operated on; in 3 animals the motor cortex (area 4) was removed, in 1 the postcentral gyrus and adjacent portion of the parietal lobe were extirpated and in 2 combined lesions of the central gyri were made. After from nine to eighteen weeks selected sections were taken from both sides of the mesencephalon, the pons, the medulla and each of the four regions of the cord, embedded in paraffin and stained with protargol (protein silver). In each specimen the pyramids of the normal and the experimental side were measured for square area and the fiber components were compared.

Extirpation of the Betz cell region (area 4) caused degeneration of only a portion of the fibers within the pyramid. In a typical monkey the affected pyramid was 13 per cent smaller than normal and possessed 68 per cent as many axis-cylinders. More extensive lesions extending in front of and behind the central sulcus failed to cause complete degeneration of the pyramids, and it is the impression of the author that the parietal cortex contributes few, if any, fibers to the pyramidal system. In none of the medullas of the 6 monkeys could any trace be found of either a circumolivary or a recurrent Pick's bundle, and no evidence of a ventral corticospinal tract was seen in the spinal cords.

Lassek's observation that about two thirds of the pyramidal fibers were intact after destruction of area 4 is in accord with the results of other investigators on the rabbit, cat, monkey and dog. The fibers lost were mainly of the large myelinated type. The view that the Betz cells give sole origin to the fibers of the pyramidal tract has been based almost entirely on results drawn from retrograde experiments, and the author questions the validity of these conclusions for several reasons. Furthermore, numerical studies have shown that the large motor cells of area 4 could not possibly account for more than 2 or 3 per cent of the fibers within the pyramids. It is difficult to see how the large Betz cells could give origin to the small myelinated and unmyelinated fibers which comprise a substantial portion of the pyramids.

CHODOFF, Langley Field, Va.

EFFECT OF ALKALOSIS AND ACIDOSIS ON CORTICAL ELECTRICAL ACTIVITY AND BLOOD FLOW. ALBERT J. LUBIN and J. C. PRICE, J. Neurophysiol. **5**:261, 1942.

It has been generally believed that changes in cortical potentials associated with variations in carbon dioxide tension have been the result of the concomitant "alkalosis" and "acidosis." In these experiments on 12 cats, intravenous injections of hydrochloric acid and of sodium carbonate sufficiently large to alter the respiratory rate failed to disturb the cortical potentials significantly. The authors suggest that changes produced by increasing or decreasing the carbon dioxide tension of the blood are related to the effect of carbon dioxide itself rather than to the resultant change in hydrogen ion concentration of either the blood or the tissues.

Effects on the pial arteries were photographed through a lucite window in the skull of each animal. The acid tended to dilate the capillaries and the base to constrict them. There was no apparent relationship between these changes and the cortical potentials.

DRAYER, Philadelphia.

ORIGIN, CONDUCTION AND TERMINATION OF IMPULSES IN DORSAL SPINOCEREBELLAR TRACTS OF CATS. HARRY GRUNDFEST and BERRY CAMPBELL, J. Neurophysiol. **5**:275, 1942.

Grundfest and Campbell studied electrical activity along the dorsal spinocerebellar tract of cats. Stimuli were delivered to peripheral nerves of the hindlimbs and to the tract itself. Contralateral stimuli evoked no impulses. The fibers in this tract are larger than those in the fasciculus gracilis, and impulses travel along it nearly twice as rapidly. There is a delay of five-tenths to nine-tenths millisecond, after the primary impulses arrive in the collaterals to Clarke's column, but the difference in rate of travel allows the impulses along Flechsig's tract to

reach the medulla more than one millisecond earlier than the corresponding impulses along the fasciculus gracilis.

Conditioning by stimulation of other afferent pathways was observed. "The electrical data indicate that the cells of origin of the fibers of the tract receive collaterals from more than one primary sensory neuron, and evidence also points to their activation by internuncial chains of varying degrees of complexity."

Responses in the cerebellar cortex were considerable. The early components were found to be "largely or entirely due to the mediation of impulses from Flechsig's tract."

DRAYER, Philadelphia.

INTERFERENCE FACTORS IN DELAYED RESPONSE IN MONKEYS AFTER REMOVAL OF FRONTAL LOBES. ROBERT B. MALMO, J. Neurophysiol. **5**:295, 1942.

After bilateral removal of the frontal association areas, monkeys succeeded in delayed response performance when darkness was maintained during the delay interval. Unlike normal animals, however, these animals failed in the test when a bright light was turned on in the cage during the delay interval. The indirect method of delayed response was used throughout the experiment; that is, light instead of food was used as the cue stimulus.

These results make necessary the revision of previous theories concerning the functions of the frontal association areas. The hypothesis is suggested that removal of the frontal association areas in primates leads to impairment in the general capacity for memory, because the loss of these areas renders them more susceptible to retroactive inhibition.

DRAYER, Philadelphia.

OBSERVATIONS IN HYPOGLYCAEMIA: III. C. S. F. SUGAR AND COMA. W. MAYER-GROSS and F. BERLINER, J. Ment. Sc. **88**:82, 1942.

These studies were based on determinations of sugar in 35 specimens of cerebrospinal fluid obtained from 6 patients. To avoid the influence on the blood sugar of the stimulus of the lumbar puncture, samples of blood were generally taken ten to twenty minutes before the spinal puncture and the sugar levels of these specimens determined. The sugar curves for the two mediums tended to be parallel, with some delay in the increase of the cerebrospinal sugar. In these cases hypoglycemic coma was no more dependent on a low sugar level in the cerebrospinal fluid than it was on a low level in the blood.

DRAYER, Philadelphia.

FURTHER OBSERVATIONS ON SODIUM AMYTAL EXPERIMENTS. F. REITMANN, J. Ment. Sc. **88**:122, 1942.

The experiments reported in this paper deal with the reactions of 30 psychiatric patients, chiefly neurotic to intravenous injections of sodium amytal. The effects on the blood sugar levels were studied. It was found that the psychologic effects of sodium amytal were accompanied by slight hyperglycemia. In some cases there was temporary depression of the dextrose tolerance curve. The author suggests that these facts are in support of the belief that sodium amytal has a direct action on the hypothalamic centers, and does not simply release these nuclei by depression of the cortex.

DRAYER, Philadelphia.

Neuropathology

SUPRASELLAR TUMORS RELATED TO THE PARS INTERMEDIA OF THE HYPOPHYSIS. W. G. MACCALLUM, Arch. Path. **34**:13 (July) 1942.

In the adult the cells of the pars intermedia can be distinguished from those of the more specialized anterior lobe. Its cells are often in irregular clumps, frequently forming small cysts with a colloid content. Occasionally the lining cells present a more cylindric form with some evidence of cilia on their free surfaces.

Often the cells extend into the posterior lobe and are scattered along the stalk up to the base of the third ventricle, where they are closely connected with the pars tuberalis.

The tumor from these cells forms a mass which extends above the diaphragma sella, although it may extend down and compress the hypophysis and partially surround its stalk. The further growth, within a capsule, projects upward and forward so as to compress the optic chiasm and one or both optic nerves; thence it extends into the floor of the third ventricle and upward so as to occupy the cavity of the latter and destroy the fornix and surrounding structures.

The symptoms produced are almost identical in all cases: bilateral hemianopia and often complete blindness in one eye, weakness, loss of libido and beginning obesity.

The surgical treatment has consisted of incision into the capsule and curetting of the contents.

Microscopically the cells are alike throughout. They tend to be cylindric, around capillaries, and often there are slightly irregular spaces between the strands of such cells. No stain brings out anything specific in the nature of granules. The tumor must be distinguished from chromophobe adenoma of the hypophysis. Usually the lesion is located within the anterior lobe, seldom reaching the capsule.

The author has suggested that the Cushing syndrome is due to a nodule of pars intermedia within the anterior lobe, but this has been "violently contradicted."

WINKELMAN, Philadelphia.

FIBROSARCOMA OF ARACHNOIDAL ORIGIN WITH METASTASES. WILLIAM O. RUSSELL and ERNEST SACHS, Arch. Path. **34**:240 (July) 1942.

Russell and Sachs report 4 cases of a malignant intracranial tumor believed to have its origin in arachnoidal cells. Only 4 cases of a similar kind were found in the literature. Of the authors' 4 cases, metastases into distant organs occurred in 3, and in the fourth case invasion of blood vessels by tumor suggested metastases, but these could not be found.

The tumors were closely related to arachnoidal fibroblastoma but were characteristic of fibrosarcoma, a malignant mesodermal tumor showing a type cell which resembled a fibroblast and produced collagen and reticulum. The authors suggest the term arachnoidal fibrosarcoma for this type of lesion.

Only 1 case need be cited. In a woman of 38, who had had an intracranial tumor removed thirteen years before, abdominal symptoms developed. At operation the surface of the liver was observed to be "covered with grayish white nodules of tumor." The histopathologic diagnosis was fibrosarcoma. The hepatic lesion was considered to have metastasized from the original cerebral tumor.

WINKELMAN, Philadelphia.

ENCEPHALOMALACIA WITH CAVITY FORMATION IN INFANTS. LEWIS D. STEVENSON and LILLIAN E. MCGOWAN, Arch. Path. **34**:286 (July) 1942.

Stevenson and McGowan describe their observations on 7 infants with what they term "encephalomalacia with cavity formation," mainly within the white matter. The cause is unknown; in 3 of their cases the Wassermann reaction was positive. The condition does not depend on thrombosis of venous sinuses, on an arterial abnormality of the brain or on encephalitis.

It was present at birth, and the clinical picture developed shortly thereafter. There is no characteristic clinical syndrome, but the condition can be diagnosed during the life of the infant by encephalogram, which shows enlargement of the ventricles and in many cases filling of the subcortical cavities with air.

WINKELMAN, Philadelphia.

A Circumscribed Arachnoid Sarcoma of the Cerebellum. B. Marquardt, Ztschr. f. d. ges. Neurol. u. Psychiat. **171**:117 (Feb.) 1941.

The author adds a fourth case of arachnoid sarcoma to 3 previously reported by Foerster and Gagel. The patient, a 43 year old woman, had a sudden onset of the illness, with severe occipital headaches. These disappeared but recurred about a month later, with intensification of the pain on bending. They were not relieved by lying down. Dizziness and occasional nausea were noted when she was off the bed. About four months after the onset she lost consciousness a few hours after a skiing accident. The next day the occipital headache recurred. Shortly before admission her gait was noted as unsteady. On admission she complained of pain in the head on moving it backward; she held her head stiffly; there was slight nystagmus on right horizontal gaze; the edge of the left disk was blurred; there were mild ataxia in the finger to nose test on the left side and some unsteadiness in the heel to knee tests; she fell backward and to the left in the Romberg test. A ventriculogram showed pronounced internal hydrocephalus with dilatation of the third ventricle. The fourth ventricle and the aqueduct of Sylvius were not seen. Death followed operation.

A soft white tumor, the size of a plum, was observed in the region of the vermis. The cerebellum was indented at the site of the tumor, which was readily removed. The meninges around the tumor seemed thickened. Histologic examination revealed a sarcoma with extension of the tumor tissue into the cerebellar cortex. Two types of cells were seen—a smaller, deeply staining lymphocyte-like cell, with a poorly delineated nucleus and cell membrane, and a larger, poorly staining, oval cell, with a clear nucleus and cell membrane. These cells showed a tendency to infiltrate the adventitial layer only. Differential stains showed no glia cells or fibers and no ganglion cells or axis-cylinders. There were no gitter cells. Reticular fibers were present.

Savitsky, New York.

Characteristic Alterations in Ganglion Cells in Cases of Hepatolenticular Degeneration and Other Hepatocerebral Diseases. N. W. Konowalow, Ztschr. f. d. ges. Neurol. u. Psychiat. **171**:229 (Feb.) 1941.

Konowalow previously described (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **169**: 220, 1940) alterations in astrocytes which account for the Alzheimer glia cells associated with pseudosclerosis. He now describes similar changes in the ganglion cells, which he observed to be extensive in 3 of 8 cases of hepatolenticular degeneration. The cell changes were encountered especially in the large cells of the striatum, in the medial and central nuclei of the thalamus, in the pontile nuclei and in the deeper layers of the cerebral cortex. The cell nucleus was enlarged to about twice its size, while the protoplasm was broken down and showed chromatolysis. In some cells the nuclei seemed inordinately large because of the breakdown of the cell body, but in most there was actual enlargement of the nucleus. Another, less frequent, change in the ganglion cells was the disappearance of the chromatin in the nucleus, with relative intactness of the cytoplasm.

Savitsky, New York.

Lipoma of Corpus Callosum. Horst Merkel, Ztschr. f. d. ges. Neurol. u. Psychiat. **171**:269 (Feb.) 1941.

Merkel reports the case of a woman of 57 who died of pemphigus. There were no mental or nervous symptoms during life. Necropsy revealed widespread pemphigus, bronchopneumonia, lipomatosis and a lipoma lying on the left side of the corpus callosum. This tumor could be followed from the rostrum to the region of the splenium, around which it wound itself. It was then observed to be connected with a yellow-white mass of fat tissue in the choroid plexus. The lipoma was 7 mm. wide anteriorly and 6 mm. wide posteriorly. It was distinct from the surrounding brain tissue. There was also some fatty tissue in the region of the chiasm.

Microscopic examination showed, in addition to fat cells, a considerable amount of collagenous tissue. This connective tissue extended even into the corpus callosum, especially its posterior portion. A few fat cells were also seen within the tissue of the corpus callosum. There was no developmental defect of the callosum itself.

The author agrees with Krainer, who maintained that lipomas of the corpus callosum are due to developmental defects. Some of the embryonic meningeal tissue fails to differentiate. The presence of this tumor tissue in the corpus callosum is in support of the hypothesis that the corpus callosum is formed by the fusion of structures coming from both cerebral hemispheres.

Twenty-four other cases of lipoma in the region of the corpus callosum were collected, in only 7 of which there were no definite developmental defects of the corpus callosum.

SAVITSKY, New York.

Psychiatry and Psychopathology

A STUDY OF FRONTAL LOBOTOMY: NEUROSURGICAL AND PSYCHIATRIC FEATURES AND RESULTS IN 22 CASES WITH A DETAILED REPORT ON 5 CHRONIC SCHIZOPHRENICS. EDWARD A. STRECKER, HAROLD D. PALMER and FRANCIS C. GRANT, Am. J. Psychiat. **98**:524 (Jan.) 1942.

Strecker, Palmer and Grant report the results of frontal lobotomy on psychotic patients. It is their opinion that this drastic procedure should be used only as a last resort. They conclude that a year should elapse after operation before one makes even a preliminary judgment as to the result. Twenty-two patients were studied, including 16 with agitated depression, 5 with schizophrenia and 1 with a sex problem. There were 2 operative deaths, 1 as the result of anesthesia and the other from postoperative hemorrhage. Both deaths occurred in the group with agitated depressions. Twelve of the 16 patients comprising this group were sufficiently recovered to leave the institution, and only 1 failed to show some improvement. Palmer notes that patients with agitated depressions showed not only diminution in agitation and loss of the affective disturbance but unwillingness to review the thought content present during the psychosis. Two of the 5 schizophrenic patients were sufficiently recovered to leave the institution; the other 3 were improved. Strecker points out that complete recovery must not be expected in the stormy, violent, destructive, aggressive type of schizophrenia such as characterized the group in this study. The postoperative reeducation and rehabilitation of patients are considered to be of the utmost importance.

FORSTER, Boston.

A MODIFIED RORSCHACH TECHNIQUE FOR THE DESCRIPTION OF TRANSITORY POST-CONVULSIVE PERSONALITY STATES. EDWARD J. STAINBROOK, Rorschach Research Exchange **5**:192 (Oct.) 1941.

Because controlled convulsion conditions make possible a closer investigation of personality reintegration after a severe convulsive crisis, psychiatric utilization of therapeutic convulsions has increased greatly.

In order to obtain a "cross section" description of the personality at various times during the recovery process, a modification of the Rorschach test has been devised. This modified test makes it possible to obtain a Rorschach psychogram of personality reactions as early as five minutes after a convulsion. In this modified test the patient is subjected to cards I, II and III as soon as he is able to respond, and then is presented with these same cards in the same order throughout the following hour. On the next day of treatment the same procedure is followed with cards IV, V and VI. On the following treatment day cards VII, VIII, IX and X are presented in the same fashion. In this way responses to all cards are assembled into composite Rorschach records for each five minute period after the convulsion. During the immediate postconvulsive half-hour, when the

responses generally show the greatest change, the maximal number of "cross sectional" profiles can be obtained.

In studying Rorschach reactions after subconvulsive electric shock and in a few cases of major convulsions, cards III, V and X were used—card III for its frequent evocation of movement responses, card V for its popular form frequency and its compact unitary form and card X for its color and detail. A similar study is being made with Klopfer's technic of "testing the limits" as an additional means of obtaining a description of postconvulsive reactions.

MARCOVITZ, Philadelphia.

A SURVEY OF THE RESULTS OF INTELLIGENCE TESTS IN PSYCHOSIS. M. B. BRODY, Brit. J. M. Psychol. **19**:215, 1942.

Brody reviews in detail reports of results of mental tests in cases of the psychoses, with almost exclusive emphasis on intelligence tests and those of cognitive functions. To aid in the evaluation of these results, he first summarized the recent observations on the normal changes in mental ability after early maturity. Ability in vocabulary tests and closely related tests, such as defining abstract words, remains stationary or increases in later life. Decline is apparent in the responses to most other tests, particularly after the fifth decade.

In cases of psychoses mental tests show that vocabulary ability is best maintained, verbal ability next, while nonverbal test ability is severely impaired. The vocabulary rating can be a measure of the patient's initial ability. It is important, since like patterns can result from different causes, to interpret each test record separately and individually, carefully evaluating the extent of the failure against the normal failure for that age and analyzing the degree of cooperation which may be interfered with by invalidating disorders of mood or stream of mental activity.

Brody believes a genuine decline in ability or dementia occurs with organic psychoses. The same pattern of failure in biogenic psychoses is more often due, however, to "pseudodementia," i. e., to disorders of mood, etc.; the mental level is quantitatively intact, while its function is interfered with.

The qualitative aspects of mental test performance are described in some detail. Some of the observations include inertia of functioning, weakness in the directional control of thought, impairment of "planfulness" and, in schizophrenia, a childlike associative type of thought, with the special qualities of asyndesis, metonymic distortion and interpenetration.

He describes the use of mental tests by some workers for prognosticating the value of shock therapy or for testing its results.

ALLEN, Philadelphia.

HYPERTHYROTIC CATATONIA: A SCHIZOPHRENIC SYMPTOM-COMPLEX. R. E. HEMPHILL, J. Ment. Sc. **88**:1, 1942.

Hemphill studied the distribution of goiter among 4,750 patients with mental disease. No patient with early schizophrenia had a nontoxic goiter. Hyperthyroidism was found to be rare in schizophrenic persons, but when it occurred it was always associated with a particular form of reaction, characterized by "a period of varying schizophrenic symptoms with auditory hallucinations, an acute episode when visual hallucinations appear, with distortion of the body-image, inability to differentiate clearly parts of the body and other evidences of instability of the boundaries of the ego. This phase is succeeded by catatonic stupor. In severe cases the end result is dementia, in others towards recovery with repetition of the cycle."

Hemphill compares this "hyperthyrotic catatonia" to the periodic catatonia described by Gjessing and concludes that there are types of schizophrenia which appear to be derived from special endocrine disorders. Systematic determination of every assayable hormone early in these illnesses may provide a clue to their cause.

DRAYER, Philadelphia.

THE PROGNOSTIC FACTORS OF ADOLESCENT PSYCHOSES. A. BARHAM CARTER, J. Ment. Sc. **88**:31, 1942.

Carter studied 78 cases of adolescent psychosis. Favorable factors seemed to be some soundness of stock, often associated with a pyknosomatic physique; a helpful environment; severe, acute psychotic episodes, and preservation during the psychosis of "normal," though possibly exaggerated, emotional reactions. On the other hand, an insidious onset, dissociation of emotional reaction, increasing withdrawal from the environment and persistence of symptoms were all indications of a poor prognosis. Particularly unfavorable symptoms were chronic catatonia, stereotypy and grotesque behavior.

DRAYER, Philadelphia.

ELECTRO-ENCEPHALOGRAPHY IN CASES OF MENTAL DISORDER. W. GREY WALTER, J. Ment. Sc. **88**:110, 1942.

Walter reports the results of electroencephalographic studies on 72 patients with various types of mental disorder. The records of patients with epilepsy, cerebral atrophy, organic cerebral lesion and catatonic schizophrenia showed definite abnormalities. Patients with other types of schizophrenia and the affective psychoses had records within normal limits. The author concludes that the electroencephalogram may be helpful in discriminating between organic and purely mental disorders. He suggests that the unusual features in the records of persons with a catatonic schizophrenia may reflect abnormalities in the electrical resistance of the tissues superficial to the brain.

DRAYER, Philadelphia.

THE INVESTIGATION OF PERSONALITY IN PATIENTS TREATED BY PREFRONTAL LEUCOTOMY. E. L. HUTTON, J. Ment. Sc. **88**:275, 1942.

In this preliminary report, Hutton suggests that in those mental disorders apparently benefited by prefrontal leukotomy (melancholia, anxiety states, obsessional and compulsive neuroses and schizophrenia) "the patient fails to attend to the real world around him, his attention being devoted almost exclusively to the autistic maintenance of those ideas and images out of which he creates the illusory world in which he lives, his actions being determined in accordance with his fantastic beliefs and not with the demands of reality." After leukotomy such autistic thinking is interrupted, and the patient responds directly to stimuli from the real environment. Associative memory, based on long-established patterns of behavior and thinking, seems to be relatively undisturbed by the operation. Hence, as long as such patients do not have to initiate the thinking, and are responding only to the thoughts of others, they appear to be as "intelligent" as they were prior to their illness.

DRAYER, Philadelphia.

PSYCHIATRIC SYNDROMES FOLLOWING BLAST. E. W. ANDERSON, J. Ment. Sc. **88**:328, 1942.

Anderson discusses the problems involved in determining what may rightly be considered the effects of blast. Especially difficult to obtain are accurate accounts of the incident. In only 2 of the 8 cases described was it reasonably certain that there had been no associated head injury of the ordinary type. The fatigue and excitement attendant on combat situations, as well as the absence of trained observers in most instances, prevent accurate study of the immediate reactions to high explosives. Lest transitory evidences of organic damage become obscured and lost, early reference of such patients to a competent psychiatrist is recommended.

Forgetfulness, difficulty in concentration and general slowing down of motor functions were found to be characteristic of this series. Affective lability for a time after the explosion was described by some patients, but apathy was a more common reaction. A fortnight's rest in bed with proper sedation is regarded as the best treatment.

The author proposes that in legal action, because of the present incompleteness of knowledge, an amnesic patient who has been exposed to a blast should be given the benefit of whatever doubt may exist as to an organic basis for his defect.

DRAYER, Philadelphia.

DRUGS AND MENTAL DISEASE. MERRILL MOORE, ALICE F. RAYMOND and M. G. GRAY, Confinia neurol. **4**:238, 1942.

Of 115,845 admissions to the mental disease hospitals of Massachusetts during the period between 1917 and 1937, there were 841 cases of mental illness associated with the excessive use of drugs. The conditions in these cases were diagnosed either as "psychosis due to drugs and other exogenous toxins" or as "drug addiction without psychosis." Thus, the admissions due to drugs and chemical agents represent an average of 0.7 per cent of all admissions during the period reviewed. In the 841 cases of mental illness associated with drugs and chemical agents, the order of frequency of the agent was as follows: opium derivatives, 363 cases; barbiturates, 208 cases; bromides, 101 cases; others sedatives, 27 cases; analgesics, 15 cases; gases, 19 cases; metals, 18 cases. There were 54 cases of addiction to miscellaneous and unidentified substances, and in 36 cases the disease was not verified as due to drugs or chemical substances.

The authors noted a higher incidence in the group of persons with college educations and those coming from the marginal economic level than among the general group of patients admitted to mental disease hospitals. A larger percentage of these patients were native-born residents, and there were more naturalized persons than aliens. There was a higher percentage of unmarried persons in the group studied than in the general population of the state or in the total number of patients admitted to the Massachusetts mental disease hospitals. The recovery rate for patients with mental disease due to drugs is high and the death rate low. The immediate prognosis of mental illness due to drugs is more favorable than that for other types of acute mental disorders. It is not possible to determine from these data whether mental disease due to drugs is increasing or decreasing.

DEJONG, Ann Arbor, Mich.

Cerebrospinal Fluid

THE GROUP OF DEMENTIA PRAECOX PATIENTS WITH AN INCREASE OF THE PROTEIN CONTENT OF THE CEREBROSPINAL FLUID. WALTER L. BRUETSCH, MAX A. BAHR, JOSEPH S. SKOBBA and WILLIAM J. DIETER, J. Nerv. & Ment. Dis. **95**:669 (June) 1942.

The authors studied the spinal fluid of 1,281 of patients with dementia praecox. Quantitative protein determinations, Pandy and Ross-Jones tests, cell counts and colloidal gold and Wassermann tests were performed. Among 634 newly admitted patients, the protein content of the spinal fluid was above 45 mg. per hundred cubic centimeters in 15 (4.4 per cent) and in 8 females (2.7 per cent). Among the old patients there was an increased protein content of the spinal fluid in 5.9 per cent of the males and 3.7 per cent of the females. None of the patients had a positive serologic reaction. There was little variation in the protein content in those cases in which repunctures were made at intervals. No clinical features were characteristic of the patients with increased spinal fluid protein. The authors speculate on the possible relationship of the cases with an increased protein content to cases of acquired cerebral syphilis of the meningovascular type and to cases of congenital syphilis, since it is known that the only observable abnormality of the spinal fluid in such cases may be a slightly increased protein content of the spinal fluid. Stigmas of congenital syphilis were not found, although a recapitulation of anamnestic data indicated that in a few cases a history suggestive of parental syphilis was present. One patient with a protein content of 130 mg. per hundred cubic centimeters died four months after admission, during a period of catatonic

excitement. Necropsy observations were within normal limits except for a few meningeal areas, where a slight cellular proliferation was observed. The authors conclude that in most cases the abnormal changes in the spinal fluid could not be explained.

CHODOFF, Langley Field, Va.

LUMBAR AND CISTERNAL SPINAL FLUID: NORMAL VARIATION. ANDRÉ TEIXEIRA LIMA, FRANCISCO TANCREDI and JOÃO BAPTISTA DOS REIS, Arq. serv. assist. psicopat. do Estado de São Paulo **5**:391 (Sept.-Dec.) 1940.

Specimens of spinal and of cisternal fluid were removed from 71 patients in a mental disease hospital, none of whom had positive neurologic signs. Twelve cubic centimeters were removed by the cisternal and lumbar routes. The total protein content of the cisternal fluid varied from 0.10 to 0.26 Gm. per hundred cubic centimeters and that of the lumbar fluid from 0.12 to 0.44 Gm. The lumbar fluid contained more protein than the cisternal fluid in 54 cases; the amounts were equal in 7 cases, and the cisternal fluid contained more in 8 cases. The authors consider the normal number of cells in the fluid to be 0 to 3 cells per cubic millimeter. There is a tendency for more cells to be present in the lumbar fluid. The ratio between the amount of protein in the lumbar and that in the cisternal fluid was 1 or more, but never over 3.

SAVITSKY, New York.

CREATININE CONTENT OF CEREBROSPINAL FLUID. JOÃO BAPTISTA DOS REIS, HANS SCHMIDT and ALAN LARA WILLIAMS, Arq. Serv. assist. psicopat. estad. São Paulo **6**:243 (Sept.-Dec.) 1941.

The authors used the Pulfrich (photometric) modification of the Folin method in studying the creatinine content of the spinal fluid. It was found that the presence of protein did not in any way affect the determination of creatinine. The amount of creatinine in the cisternal fluid of 100 patients in a mental disease hospital who had no organic disease varied from 0.87 to 1.48 mg. per hundred cubic centimeters. In most cases (32) 1.06 to 1.14 mg. was noted. In 50 cases simultaneous determinations of creatinine were made on the blood and on the spinal fluid. The ratio of creatinine in the spinal fluid to that in the blood was always less than 1. The values for the spinal fluid varied from 47 to 96 per cent of the creatinine in the blood and in most cases from 70 to 80 per cent. In 10 cases simultaneous lumbar and occipital punctures were made, and the amounts of creatinine in the two types of fluid were compared. The creatinine content of the lumbar spinal fluid in 9 cases was less than that of the cisternal fluid. In 1 case the level of creatinine in the cisternal and that in the lumbar fluid were the same.

SAVITSKY, New York.

Muscular System

POTASSIUM AND MUSCULAR DISORDERS. J. N. CUMINGS, J. Neurol. & Psychiat. **4**:226 (July-Oct.) 1941.

Cumings found no abnormality in the potassium content of muscles or any therapeutic effect of prostigmine in the majority of muscle diseases and in conditions in which fat or fibrous tissue replacement of muscle occurs. However, in a patient with a parathyroid tumor there seemed to be an association between the muscular weakness and the low potassium level in the muscles. Two patients with severe myasthenia gravis, who were receiving a diet resulting in a positive potassium balance, were studied. As in previous experiments, injections of prostigmine methylsulfate liberated potassium from muscles, resulting in an increase of potassium in the serum. In addition, the author found that red blood cells also showed an increase in potassium content. Therefore, the increase in the total potassium content of the blood accounted better for the liberated muscle potassium than the serum alone. There was no increase of potassium in the urine after injection of prostigmine. Division of motor nerves to muscles in patients, as well

as in experiments with animals, did not affect the potassium content of the muscles. Cumings concludes that an abnormality in potassium content of muscles is primarily associated with myasthenia, although it may not actually cause the disease. The author was unable to produce muscular disorders in rabbits with substances extracted from the roots of American and Chinese varieties of yellow jasmine.

MALAMUD, Ann Arbor, Mich.

THE EFFECT OF PROSTIGMIN ON THE URINARY EXCRETION OF POTASSIUM IN THE NORMAL SUBJECT. J. N. CUMINGS, J. Neurol. & Psychiat. **4**:235 (July-Oct.) 1941.

In cases of myasthenia gravis, injections of prostigmine methylsulfate liberate potassium from the muscles into the blood, but the urine shows no increase in the amount of potassium. Studies on 3 normal subjects showed that injection of prostigmine had no effect on the excretion of potassium in the urine. This offers further proof that prostigmine is not the direct cause of the retention of potassium in patients with myasthenia.

MALAMUD, Ann Arbor, Mich.

THE FREQUENCY, ETIOLOGY AND PROGNOSIS OF EYE MUSCLE PALSIES. E. KESSLER, Confinia neurol. **4**:159, 1942.

Kessler has prepared a statistical study of the frequency, etiology and prognosis of palsies of the ocular muscles, basing her conclusions on 233 cases. Paralysis of the internal branch of the oculomotor nerve and of the levator palpebrae superioris and paralysis of associated movements were excluded. The abducens nerve was most frequently involved, followed by the external branches of the oculomotor nerve and then by the trochlear nerve. Ocular palsies were observed twice as frequently in men as in women. Etiologic factors were listed in the following order: fracture of the skull, apoplexy, congenital paralysis, trauma to the orbit, multiple sclerosis, brain tumor and syphilis. Ocular palsies were observed most frequently from the third to the sixth decade. The prognosis of ocular palsies following fracture of the skull or apoplexy is relatively good; more than half of all the patients recovered or showed improvement.

DEJONG, Ann Arbor, Mich.

Congenital Anomalies

COMBINATION OF FRIEDREICH'S ATAXIA AND CHARCOT-MARIE-TOOTH ATROPHY IN EACH OF TWO BROTHERS. ALEXANDER T. ROSS, J. Nerv. & Ment. Dis. **95**:680 (June) 1942.

Ross points out the rather close relationship existing in certain cases between Friedreich's ataxia and peroneal muscular atrophy of the Charcot-Marie-Tooth type. Cases partaking of the characteristics of both these syndromes have been described by many investigators. Ross reports the cases of 2 brothers presenting a combination of these two conditions. A sister had undoubted Friedreich's ataxia, and a maternal cousin was a high grade moron with signs of mild involvement of the pyramidal tract and "Friedreich feet." One of the brothers reported was a moron with slurred speech, bilateral weakness of the external rectus muscles, nystagmus, bilateral cerebellar signs, weakness and pronounced atrophy of the peripheral musculature of the extremities, absence of deep reflexes and diminution to loss of all modalities of sensation in a glove and stocking distribution. Examination of the other brother gave similar results, with a more pronounced degree of mental defect.

The observations on this family lend support to the belief that the neurologic heredodegenerative diseases represent abiotrophies of certain parts of the nervous system, which in individual cases may manifest themselves in isolated, abortive or bizarre combinations. The relation of these cases to the syndrome of Roussy and Lévy and to the familial spastic paraplegias is discussed.

CHODOFF, Langley Field, Va.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

ABRAHAM A. BRILL, M.D., *President, New York Neurological Society, Presiding*
Joint Meeting, May 5, 1942

The Electroencephalogram in Epilepsy. DR. FRANCIS A. ECHLIN.

The present work is based on an electroencephalographic and clinical study of 100 cases of epilepsy.

The merits of the Gibbs-Lennox (ARCH. NEUROL. & PSYCHIAT. **39**:298 [Feb.] 1938) and the Jasper-Kershman electroencephalographic classification of the epilepsies are discussed.

The work to be presented is based on the Jasper-Kershman classification (ARCH. NEUROL. & PSYCHIAT. **45**:903 [June] 1941), which was found to be the most satisfactory for the routine study of epileptic patients, especially since most patients must be studied between seizures.

Technic.—A four channel, ink-writing electroencephalograph apparatus, built by Rahm, was used throughout the study. Electrode placements were the same as those described by Jasper, Kershman and Elvidge (ARCH. NEUROL. & PSYCHIAT. **44**:328 [Aug.] 1940). One hundred and ninety electroencephalograms taken from the 100 patients were studied. The work was done in the neurologic and neurosurgical service of Lenox Hill Hospital.

Summary of Results.—The characteristic feature of the records was the recurrent or paroxysmal appearance of high voltage waves, a phenomenon which Jasper and Kershman called paroxysmal hypersynchrony (exemplified in the first two groups to be described later). Most of these discharges occurred at frequencies which may be regarded as abnormal, and therefore, in addition to hypersynchrony, there was usually dysrhythmia, as described by Gibbs, Gibbs and Lennox (*Brain* **60**:377, 1937).

In attempting to classify the records, I, like Jasper and Kershman, found that this could best be done on the basis of localization studies, and cases were grouped according to the site of the abnormal discharges in the brain. The different wave forms and patterns were of considerable help in the analysis of individual cases, but were of secondary importance, especially in cases in which a focal abnormality was present.

Analysis of the electroencephalographic records without reference to other data revealed that they could be divided, according to the Jasper-Kershman classification, with a considerable degree of accuracy into four groups.

Localized unilateral cortical abnormality (30 cases). The wave forms and patterns encountered were: random spikes, 2 cases; random sharp waves, 24 cases; random delta waves, 4 cases, and paroxysmal rhythmic discharges, 5 cases, the last being also included under sharp wave forms. It should be noted that these so-called localized discharges may at times cover a large area of one hemisphere.

Bilaterally synchronous abnormality from homologous areas in the two hemispheres (35 cases). The wave forms and patterns present were: 3 per second wave and spike patterns, 7 cases; sharp waves, 14 cases; 3 per second waves, 13 cases, and 6 per second waves, 5 cases, 4 of which were placed in the sharp wave group as well.

We agree that the 3 per second wave and spike pattern and the 3 per second wave form seem to originate from a deep midline pacemaker. The sharp wave discharges appear at times to arise deep in one temporal lobe and to be transmitted as a "mirror" focus to the opposite hemisphere.

Diffuse, nonlocalized abnormality (15 cases). This type of abnormality was characterized by disorganization of the alpha rhythm, variation in amplitude and frequency of the cortical rhythms, but without hypersynchrony (as in the first two groups), and scattered delta activity of low amplitude. These observations differ from those of Jasper and Kershman.

Normal electroencephalograms (20 cases). It was at times difficult to distinguish between a record showing a slight diffuse abnormality and a normal electroencephalogram.

Illustrations of the various types of abnormality are shown. A combined analysis of the clinical data and the electroencephalograms is now presented.

Localized unilateral cortical abnormality (30 cases). In 70 per cent of the cases in which this type of electroencephalogram occurred there was a clinical history of focal epilepsy; that is, the pattern of the attacks suggested a focal cortical origin similar to that indicated in the electroencephogram. In 53 per cent of these cases the presence of a pathologic lesion was proved by air studies, operation or postmortem examination of the region of the cortex indicated in the electroencephalogram. An analysis of the different types of clinical seizures and their relation to wave forms and patterns is presented. Attacks of the petit mal variant and the psychomotor type were not uncommon.

Bilaterally synchronous abnormality (35 cases). In 92 per cent of these cases generalized grand mal seizures were present without any clinical pattern to suggest an origin in a focal area of the cortex. The initial symptom was usually loss of consciousness, which was in keeping with an origin in a deep midline area or sudden involvement of the greater portion of the cortex of both hemispheres. In 35 per cent of the cases petit mal attacks and in 38 per cent seizures of the petit mal variant or the psychomotor type occurred. The relation of the clinical attacks to the wave forms and patterns is discussed. Seizures of the petit mal variant and the psychomotor type were most common in those cases in which bilaterally synchronous sharp waves arose from the temporal lobes. In cases of a 3 per second wave and spike or a 3 per second wave pattern (20 cases) the average age at onset of seizures was 12 years, and the average age at the time of examination was 18 years.

Slight diffuse abnormality or normal electroencephalograms (35 cases). In 92 per cent of cases grand mal seizures without clinical localizing features were present. In 17 per cent there were petit mal attacks. In 20 per cent attacks of petit mal variant or psychomotor type occurred. In 14 per cent the clinical history suggested focal cortical onset. The site of origin of the seizures in these cases was hard to determine because of the relative inactivity of the abnormal focus. The average age at onset of the attacks in this group was 26 years and the average age at the time of study was 37 years. The fact that the epileptic focus in these cases was relatively inactive electrically may be related to the age of the patients, for Golla, Graham and Walter (*J. Ment. Sc.* **83**:137, 1937), in a study of 214 epileptic patients, found few abnormal electroencephalograms in persons over 40 years of age.

A classification of the electroencephalograms based on the pattern of the clinical seizure is also shown.

In summary, it may be stated that the pattern of clinical seizure shows a close relation to the form of the electroencephalogram, especially with regard to localization. The observations of Jasper and Kershman have been largely corroborated.

DISCUSSION

DR. PAUL HOEFER: I should like to say a few words about the clinical usefulness of the records of brain waves. My associates and I still use the Gibbs and Lennox classification, which, even if it may turn out to be only a working

hypothesis, has helped us a great deal, just because it is an attempt to correlate the clinical and the electrical features. It is still possible for me, at least, to use this correlation, with slight modifications.

It is significant that during clinical seizures we obtain the specific electroencephalographic patterns, except perhaps in grand mal attacks, when we see spike and wave groups in addition to the high voltage, rapid activity.

Between petit mal seizures, or perhaps I should say in the absence of clinically noticeable petit mal seizures, we find the synchronous 3 per second spike and wave pattern in about 85 per cent of our cases.

Between grand mal seizures, however, and during psychomotor seizures we obtain the specific seizure pattern in only 55 to 60 per cent of our cases, and in an additional 20 per cent of the cases we find patterns attributed to another form of seizures, such as the grand mal pattern in cases of psychomotor epilepsy and vice versa. In another, smaller group of cases of grand mal seizures we find only a spike and wave pattern, as does Dr. Echlin.

There are several possible explanations for this; it may be that in these cases there are actually brief clinical or subclinical attacks of both forms of the disease, though only the more dramatic of the two is detected clinically. It is also possible that the brain wave patterns are not as specific as was thought at one time.

As to the focal origin of the generalized seizures, we have not had the experience of the Montreal group. We have found these foci shifting, and I know of cases in which after operation a focus has appeared in another part of the brain. Only in clinically strictly focal motor seizures have we found a good correlation with the brain wave record.

However, only now are the meaning of the brain waves and their relation to action potentials of brain cells and fiber tracts beginning to be understood. Electroencephalography, I believe, is the method by which the problem should be studied, and clinical interest, no matter to what school of thought one belongs, is the best stimulus to continuation of this work.

DR. MARGARET RHEINBERGER (by invitation): Perhaps the reason for my preference for Dr. Echlin's point of view lies in the fact that I have found the general clinician to be imbued with the idea that electroencephalography can tell him whether a patient has "epilepsy," by which he means what I should call functional epilepsy. I try to impress on any clinician with whom I come into contact the preferability of his avoiding the use of the clinical term with reference to the electrical patterns which are obtained. Dr. Echlin's figures, based on a study of 100 patients who had epilepsy, showed 20 per cent with normal electroencephalograms. I think my co-workers and I have about the same percentage in our records, which comprise tracings for approximately 350 epileptic patients out of a much larger group of persons with other disorders as well. About 30 per cent of all the patients who had clinical epileptic attacks and who came to our laboratory for investigation had tumor.

I should like to emphasize the point that although paroxysmal hypersynchrony is characteristic of the majority of cases of epilepsy, as Dr. Echlin has pointed out, and as I am sure Dr. Hoefer will agree, there are instances in which the clinical focus of an epileptic attack is represented electrically not by hypersynchony but by depression of amplitude, a loss or slight slowing of the normal rhythm. Such changes have not, so far, been considered in discussions on electrical patterns associated with epilepsy, and yet they cannot be ignored as indications of localized disturbance.

A case which is of interest from the point of view of localization not only of epileptic patterns but of cerebral abnormalities in general is that of a woman who came to the hospital with which I am associated with a high grade of papilledema and with no clinical neurologic localizing signs. Her electroencephalographic pattern was confusing in that from the right frontal area there was a slow wave, more or less paroxysmal discharge, not of high amplitude, while the left parietal region showed slowing of the rhythm which did not appear to be correlated with the paroxysmal discharge recorded from the frontal area. On the basis of the

electric pattern we felt we were incapable of making a decision as to which of these two changes was of greater importance. Just prior to the taking of the electrical record the patient had her first and only seizure, which involved only the left side of the body, and it was therefore assumed that the electrical change from the right frontal area was correlated with the damage which had produced the seizure. Because of this observation and the fact that whatever other clinical evidence there was pointed to the same area of localization, it was decided that she had a tumor of the right frontal region. She did not. The tumor was in the left parietal lobe, and the reason for the seizure, which was left sided, and the electrical discharge from the right frontal region was a recent hemorrhage in that area. The tumor was a meningioma, and if we had known a little more than we did we might have saved the patient's life.

Psychopathologic Review of Senile and Arteriosclerotic Disorders. Dr. Oskar Diethelm (by invitation).

It is generally accepted that memory disorders and senile personality changes, decline of judgment, disorders of comprehension and attention, disorientation and apathy form the psychopathologic reaction in senile and arteriosclerotic psychoses. With the aid of a group of psychologic tests, patients with such disorders were studied. An especially planned maze test permitted the study of orientation to a task and of memory. Persons with senile disturbances showed difficulty in orientation to a task and in learning, diminished retention and recall, shortened span of active attention, tendency to perseveration and use of grooves of thinking.

Anxiety shortens the span of active attention and diminishes retention and relearning. The presence of anxiety in senile or arteriosclerotic patients increases disorders of retention and attention and difficulty in understanding a task. Thinking disorders become especially pronounced through the presence of depressive thinking and may lead to a confusional disorder.

Minor physical ailments, found especially with arteriosclerosis (kidney and cardiovascular disease), minor infections, dietary disorders and avitaminosis, may also cause disturbances of thinking and memory, which in the past have been explained by cortical damage. The outlook in many cases of so-called deterioration may be favorable if physical treatment can eliminate these complications and psychotherapy can alleviate anxiety.

DISCUSSION

Dr. Lawrence S. Kubie: There is great difficulty in isolating the machine factor in intellectual performance from the emotional element. This is evidenced in the difficulty of testing the thinking capacity apart from the influence of the emotional background. All have encountered this problem in examining old people and have found it extremely hard to decide whether a reduction in the output of the thinking machine was due to a defect in the machine itself or to the accompanying depression or anxiety or to a combination of the two. Dr. Diethelm condensed his presentation so much that it was not clear to me how the maze test makes it possible to differentiate between the play of emotional factors and a reduction in the intrinsic efficiency of the machine itself. I wonder whether electroencephalography, when correlated with these studies, throws any light on this problem. I recall the theory that used to be advanced to differentiate between the arteriosclerotic and the senile disorders and the emphasis that Hoch laid on what he called a "mental tension" defect. By this he meant not an isolated mental function but a complex product of intellectual and emotional activities. He felt that in the arteriosclerotic patient this loss in "mental tension" was primary and that such a patient was aware of his difficulty and suffered acutely because of it. I should be interested to know whether Dr. Diethelm's studies have borne this out.

Dr. Oskar Diethelm: Dr. Kubie embarrassed me slightly when he asked about the maze test; because of the limited time for the presentation I merely mentioned that it was an essential test, but there are many others.

In cases in which my associates and I took electroencephalograms we were never able to see any clear correlation with the results of these tests.

I do not know enough about Hoch's concept of "mental tension" to discuss it. I never saw it mentioned in the literature, but from Dr. Kubie's description I think it corresponds to what one finds in some senile patients. Mental tension is hard to define, and I have never felt that Bleuler was able to define it well, either.

Cachexia of Mental Origin: Nature and Management. DR. JOHN L. SMALLDON (by invitation).

This paper constitutes a summary of a study of 6 girls at the New York Hospital, Westchester Division, whose illnesses were initiated by self starvation and the consequent development of a cachectic state. Significant similarities characterize the 6 cases. The psychopathology is stressed. Each case presents the well known history and physical signs of anorexia nervosa, but all have been considered by a number of examiners, who have observed the patients daily for months or years, to be cases of dementia praecox rather than of compulsive-obsessive neurosis. It is speculated that in some cases of compulsive-obsessive neurosis characterized by anorexia nervosa the condition will on later observation be found to have progressed beyond the realms of a psychoneurosis into a psychosis. For this reason, in addition to the fact that the term anorexia is inaccurate in describing this voluntary self starvation, it is suggested that the condition be labeled "cachexia of mental origin," rather than anorexia nervosa.

DISCUSSION

DR. LELAND E. HINSIE: The following mental factors are common to all patients: mentally induced emaciation; fear of enlargement through eating; fear of effeminacy; absence of overt sexuality; fixation at an oral and anal level, with predominance of anal trends, evidenced by excessive cleanliness or the opposite (smearing of feces), orderliness, stubbornness, hoarding and guilt over eating (oral impregnation; sexual excitation caused by intake of food); reversal of sexual role in parents, and energy prevented from entering the sexual zone and kept at anal and oral levels. The psychopathologic state was essentially preoedipean.

The physical factors common to all patients were female sex, early maturity, asthenic habitus; inadequate development of sex organs; masculine distribution of hair, and pronounced disturbances in the vegetative nervous system.

Diagnosis.—Authorities differ on nosologic classifications. Evidence favors the diagnosis of a form of psychoneurosis. Personally, I believe a reaction of this type is best understood as a compulsive-obsessive psychoneurosis, the psychopathologic basis of which is fixation of energy on oral and anal factors. I believe, also, that somatopathologic factors play an equally important role. Insight into the illness (not the nature of it) is fully retained. The projection mechanism is usually absent, and, when present, it constitutes but a small part of the total difficulty. The patients are introverted in that their attention is riveted on their physique, but they appear not to be schizoid, for they are not averse to socialization. A psychoneurotic person, asocialized because of phobias or anxieties, is not said to be schizoid. A depressed patient (of the manic-depressive type) is not said to be schizoid, though object cathexis is scanty.

The physique may be called on, so to speak, to bear the brunt of any kind of mental conflict. For example, the patient with schizophrenia of the hebephrenic or catatonic form may, and often does, put all of his primitive mentality in terms of physical functions. The language of such schizophrenic patients is a body language that speaks from the phylogenic level. The neurasthenic patient speaks from the ontogenic level, particularly from the levels of orality and anality. Mental cachexia, I believe, is closely allied to neurasthenia, which is, in turn, closely related to the compulsive-obsessive syndrome. Patients with conversion hysteria, likewise, use their physique to express a mental conflict. In these

instances the conflict issues from the genital level. I believe it would better fit current concepts to enter anorexia nervosa as a subdivision of the psychoneuroses.

Thus far there is no specific form of therapy known to influence this condition favorably.

DR. A. A. BRILL: In listening to Dr. Smalldon, and particularly to Dr. Hinsie, who emphasized that these patients direct all their energy to the oral and anal openings, it occurred to me that instead of calling the condition "mental cachexia," which in my opinion is not a description, it would be best to designate it as "gastruloid regression." I refer to Haeckel's theory of the gastraea, which consists of the outer layer, from which the skin and the nervous system develop, and the inner layer, which forms the alimentary canal and the other organs. According to Haeckel, all metazoa start as gastrulae, i. e., as beings resembling a plum with an upper and a lower gateway. As the patients described by Dr. Smalldon and others center everything on the mouth and the anus, we may look on them as phyletic reversions to the gastrula.

DR. IRVING H. PARDEE: I became interested in this syndrome because it simulates Simmonds' disease, the syndrome of pituitary cachexia. I have worked with a large number of patients with this disorder, about 20 altogether, and I should like to aline myself with Dr. Hinsie and consider the disease as a psychoneurosis. I have not seen any patients with the advanced form, such as Dr. Smalldon described. Most of the patients I have seen have been ambulatory, usually either living at home or able to go to a general hospital or the Neurological Institute for treatment. It may be that some of them are schizophrenic, but those I have seen were not.

I should like to bring out two points from the physical side. First, I do not think the amenorrhea belongs in the field of psychopathology. I believe it is the result of starvation and hormone deficiency. A friend who lives in Puerto Rico told me that when they have a period of starvation down there amenorrhea is common among women. Therefore I am not willing to subscribe to the theory that this disturbance is due to fantasies or any such psychologic factor.

Dr. Hinsie brought up the other point, that of hair growth. It is reported that in the Irish potato famine of 1858 the women were noted to grow hair on the face and body as part of the starvation situation. There is no evidence of deficiency of the pituitary, thyroid, gonads or adrenals. Excessive hair growth is usually the result of a hyperplastic disturbance of the pituitary or the adrenal glands. In this syndrome there is a deficiency of these glands, rather than otherwise, and it is a functional deficiency, secondary to starvation. No actual atrophy is present in these glands. One patient had her appendix removed in the course of her illness, and I prevailed on the surgeon to take out a portion of the ovary for examination. The tissue was normal, with normal follicles, and though she had amenorrhea, all the setup for good ovarian function was present.

I look with fear on the use of insulin in treatment of these patients. I know Dr. Smalldon used it with a number. The patients we studied carefully have all shown uniformly low blood sugar curves, and I should be afraid to give a good-sized dose of insulin for fear of bringing about too serious shock.

I wish to support what Dr. Hinsie said about the pattern these patients present. It is a uniform physical pattern. Photographs of the patients all look alike, and the same is true basically of their symptoms. Chief attention is given to the gastrointestinal tract. They will not eat because "it stops right here, doctor [illustrating], and it won't go any further," or "when I eat I feel so bloated," and so on, with the usual story of a gastric neurosis. The fundamental fact is that of the attachment to one or the other of the parents, which Dr. Smalldon mentioned, the unwillingness of the young person to grow up and be an adult. Closely linked is the adolescent, and almost infantile, attitude which the majority present toward sexual matters.

DR. HENRY ALSOP RILEY: I have read numerous articles, that of Dr. Pardee and others, and have seen a number of these patients, but I have never encountered

the condition in a male. So far as I know, I have never seen any reported cases of the syndrome in a male. Can you throw any light on that, Dr. Smalldon?

DR. FRANK J. CURRAN: I should like to know the racial background of these patients. I have seen 5 or 10 such patients in Bellevue Hospital, all adolescent girls, and it is my impression that they were all Jewish. I am wondering whether Dr. Smalldon's patients were Jewish, in view of the fact that the percentage of Jewish patients in Bellevue Hospital is usually not large.

I take exception to the speaker's using the term "mental cachexia." When I read the program I thought he might be going to talk about mental deficiency. There is a recognized name for this condition, and I think it should be used.

DR. JOHN L. SMALLDON: To answer Dr. Curran first, all of these 6 patients were of Anglo-Saxon stock; I have seen no patients with this condition among Jews.

In answer to Dr. Riley, several cases of the disease in males have been reported in the literature. Each author has referred to the fact that such cases are uncommon, and I myself have seen no males with this disease.

The question of diagnosis, or the differentiation of the reactions of compulsive-obsessive neurosis and dementia praecox is one that could be argued all night. It is sufficient to state that each of the patients here reported on has been observed daily for months or years by a number of examiners, who have unanimously agreed that each patient is suffering from a psychosis, a schizophrenic reaction.

PHILADELPHIA PSYCHIATRIC SOCIETY

ARTHUR P. NOYES, M.D., *President, in the Chair*

Regular Meeting, May 8, 1942

Subconvulsive Electric Shock Therapy: Effect of Varied Electrode Applications. DR. SOLOMON LESSE (by invitation), DR. B. H. GOTTESFELD (by invitation) and DR. H. H. HERSKOVITZ, Norristown, Pa.

In this study we attempted to evaluate subconvulsive electric shock as an agent in the treatment of the psychoses. At the same time we wished to compare the results of different electrode applications in the administration of electric shock therapy. Twenty-four patients were treated three times a week, each patient first receiving six to ten subconvulsive treatments and then ten convulsive treatments. Each subconvulsive treatment consisted of five applications given over a period of three minutes. Six patients received bifrontal applications of the electrodes, 8 patients bitemporal applications and 10 patients biparietal applications. Routine preshock studies and a postshock check-up examination, including roentgenograms of the spine, were made.

The biparietal applications required a current of the lowest voltage acting over the briefest period to produce a grand mal convulsion. The bitemporal and the bifrontal leads required, respectively, increased voltage and exposure for a longer time to produce the same effect. The subconvulsive reactions were produced by a current of minimal voltage acting over the briefest period, the average being 30 volts applied for three-tenths second.

No complications were encountered with subconvulsive therapy in our series of 24 patients, which confirms the belief that complications are materially reduced with this type of shock therapy. However, in larger series of patients complications may be demonstrated.

In order that the confusion of multiple terms, such as abortive reactions and convulsive equivalents be avoided, it is suggested that the all-inclusive term subconvulsive reaction be applied to those responses characterized by a single severe muscular contraction associated with the prolonged period of unconsciousness

(thirty seconds to fifteen minutes) and the petit mal reactions. With subconvulsive therapy, one may obtain primarily a series of petit mal reactions. However, as the voltage and the time intervals are increased the subconvulsive phenomena become more pronounced.

It seems apparent from our study that subconvulsive therapy does not produce any notable therapeutic effect. Fifty per cent of the patients had affective disorders (5 had manic-depressive psychoses; 3, agitated depressions, and 4, involutional melancholia, and none of these persons improved or recovered with subconvulsive shock doses, whereas 7 patients, or 29 per cent of the series, improved or recovered with convulsive therapy. There were 12 patients with schizophrenia —9 with the catatonic type, 2 with the simple type and 1 with the paranoid type. None of these benefited from subconvulsive treatment, while 2, or 8.3 per cent, improved with convulsive therapy (both patients relapsed soon after treatment was terminated). These results are in contrast to those reported recently by Androp (*Psychiatric Quart.* **15**:730-749 [Oct.] 1941).

Our studies further reveal that subconvulsive therapy increases the fear and apprehension patients have for electric shock treatment. Fifteen of the patients showed a definite fear reaction after the applications. Furthermore, an attempt to maintain with subconvulsive applications the improvement shown with convulsive doses failed.

Although one may try subconvulsive doses in treatment of patients with associated hypertension, advanced age, cardiovascular-renal disease or general arteriosclerosis, the results are indeed dubious. Patients may show temporary improvement in ward reactions, but even this is uncertain.

In conclusion, subconvulsive electric shock therapy is of doubtful value. None of the 24 patients in this series treated at the Norristown State Hospital improved or recovered with subconvulsive electric shock therapy, whereas 37 per cent improved or recovered under convulsive therapy.

DISCUSSION

Dr. Joseph F. Hughes: Dr. Lesse and his associates have brought important clinical facts to our attention. To obtain clinical results with electric shock therapy, sufficient strength of current must be used to produce convulsive seizures. Experience at the Pennsylvania Hospital for nervous and mental diseases is in agreement with that of Dr. Lesse in that subconvulsive doses are therapeutically ineffective.

This paper raises an important question: How does electric shock treatment stop the psychotic attack? Electroencephalographic tracings following such treatment show that the brain undergoes decided electrical reorganization. Histologic studies on experimental animals and on the brains of 2 patients (Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, Arch. Neurol. & Psychiat. **47**:385-398 [March] 1942) revealed that small petechial hemorrhages and cellular destruction occur in the brain after electric shock therapy. This observation suggests that clinical recovery results from the destructive activity of the electrical current. Such a hypothesis assumes that psychologic reactions following electric shock therapy are incidental to recovery. This hypothesis, for which I take responsibility, has some experimental observations to support it. It is useful only if it serves as a framework for further clinical and laboratory research into the problem of how electrical shock produces recovery from the psychosis. It is a step in the direction of correlating the clinical results with the observed changes in the brain.

Dr. B. H. Gottesfeld, Norristown, Pa.: A series of 27 patients treated similarly has been reported on by Kalinowsky (*New York State J. Med.* **41**:2210-2215 [Nov. 15] 1941). Although his results were not identical with the observations in our series, the general trend was practically the same, the responses of 22 patients were in complete accord with those we observed. However, 5 patients improved with subconvulsive therapy. The early report by Kaplan indicated some

improvement with subconvulsive therapy and adjunctive barbituate therapy. The observations in our series did not include the use of adjunctive chemotherapy.

DR. SOLOMON LESSE, Norristown, Pa.: One might ask why we chose to give five applications of the electrodes with each subconvulsive treatment. This was done with the hope that in this manner we should approximate the effective dose given with the convulsive application and at the same time obtain results comparable to those received with regular therapy. In other words, this mode of treatment is more or less empiric. In some instances patients had a grand mal seizure with the third or fourth application of the electrodes, which indicated a cumulative effect induced by repeated subconvulsive doses given within two or three minutes. Even this, however, did not alter our results.

Use of Adrenal Cortex Extract in Cases of Insulin Shock Complicated by Pulmonary Edema: Review of Literature and Report of a Case. DR. B. H. GOTTESFELD, Norristown, Pa. (by invitation).

The purpose of this work is to evaluate the treatment of acute pulmonary edema associated with insulin shock therapy. In a review of 272 cases of schizophrenia, acute pulmonary edema occurred as a complication in 1.1 per cent of cases in which insulin was used. The symptoms of acute pulmonary edema, as outlined by Furst and Goldman, did not follow a fixed pattern in this series. The sequence of events showed considerable variability in the neurologic signs which developed. However, the early forerunner of pulmonary edema was a decided increase in the respiratory rate, followed by labored breathing and cyanosis. There was no constant correlation between the dextrose level in the blood and prolonged coma with or without pulmonary edema.

REPORT OF CASE

C. K., a 20 year old man, had acute symptoms of schizophrenia of two months' duration. He suffered from auditory hallucinations of a condemnatory type and saw visions of God. At times he was mute and resistive. A strong depressive component was associated with his hallucinations, for which electric shock therapy was begun. Ten treatments resulted in some improvement in his adjustment in the ward.

Insulin shock therapy was begun on Nov. 11, 1941. The initial dose of 20 units was increased by 20 units daily. On the seventh day of treatment he received 135 units of insulin. At 11:10 a. m. he entered a state of wet coma, and at 11:50 a. m., without having been tube fed or given medication, he became extremely cyanotic. Almost immediately, bubbling rales could be heard throughout his chest, and frothy sputum began to escape from his mouth. His temperature rose to 105.8 F. The blood dextrose was 520 mg. per hundred cubic centimeters. The respiratory rate rose from 48 to 70 per minute, and cyanosis was extreme.

Neurologically, the patient showed bilateral Babinski and Tromner signs. The deep tendon reflexes were uniformly exaggerated, and the corneal reflexes were absent. The pupils were dilated and reacted sluggishly to light.

The plan of treatment was to administer oxygen, adrenal cortex extract, thiamine hydrochloride in large doses and supportive measures in the form of digalen and fluids as indicated. He received 10 cc. of adrenal cortex extract, divided into three doses administered at three hour intervals. Later, he received sulfonamide drugs, with the idea of preventing a complicating pneumonia.

The symptoms of pulmonary edema persisted for fifty hours, and he remained in coma for seventy-four hours. On the fourth day he began to speak, but his speech was so slurred as to be unintelligible. The Babinski sign disappeared, and the corneal reflexes returned. However, he was hypersomnolent, and the soft palate was partially paralyzed. For two weeks he appeared dazed and "washed out." Improvement was constant, and he no longer revealed any evidence of hallucinations. The Babcock-Levy test revealed an efficiency index of —5.5, and this extreme degree of pathologic inefficiency led one to believe that the

patient had sustained organic damage to the brain. The Rorschach test revealed no signs of organic disease, but indicated strong schizophrenic tendencies.

CONCLUSIONS

1. Acute pulmonary edema was found in 1.1 per cent of the patients with schizophrenia who were treated with insulin at the Norristown State Hospital.

2. The occurrence of neurologic signs with acute pulmonary edema did not, in all cases, follow the pattern associated with insulin shock therapy.

3. Adrenal cortex extract proved of value in the treatment of acute pulmonary edema and prolonged coma associated with insulin shock therapy.

DISCUSSION

DR. THURSTON D. RIVERS: I have listened with interest to the paper because in my experience I have not observed pulmonary edema as a complication of prolonged stupor.

I wonder why Dr. Gottesfeld thinks that the administration of saline solution, as well as adrenal cortex extract, to patients with this condition is beneficial. It seems to me that any increase of blood volume, with a tendency to dilate the blood vessels, would be contraindicated. The use of adrenal cortex extract will probably have some effect on the water balance, but I do not see how it would increase the ability of the cells to utilize the sugar in the blood stream.

DR. ARTHUR P. NOYES: What would you think, Dr. Rivers, of the advisability of using plasma or of the transfusion of whole blood?

DR. THURSTON D. RIVERS: Hypertonic solutions of all kinds may be useful. Whole blood has some dehydrating effect, but not a great deal. The use of dry plasma, dissolved in 50 per cent sucrose, should be beneficial

DR. SOLOMON LESSE, Norristown, Pa.: The extent of damage to the brain done by prolonged coma is still a question. Dr. Harry Zimmerman, of Yale University, has told me of a woman of 44 with schizophrenia who died after four days of prolonged coma occurring in her second course of insulin shock treatments. At autopsy her brain showed extensive destruction of the ganglion cells.

DR. THURSTON D. RIVERS: It is well to consider prolonged stupor not so much as a complication but as an extension of the desired period of coma. A patient with prolonged hypoglycemia should first be treated with dextrose if he reaches the condition in which dextrose does not seem to be restorative, other therapeutic measures, such as administration of plasma, should be instituted. Then there are persons who respond to no therapy whatever. I have been much interested in patients with prolonged coma and their recovery. In my own series I was surprised to find that only 50 per cent of the patients with prolonged coma were benefited by the coma.

DR. B. H. GOTTESFELD, Norristown, Pa.: The association of pulmonary edema and other pulmonary complications with prolonged coma is not uncommon. Jessner indicated that pulmonary complications constitute one of the more frequent types of untoward reactions to insulin treatment. As to justification for the use of saline solutions following pulmonary edema, I should like to point out that there is considerable difference of opinion. The use of plasma and whole blood has been recommended. The theory that there is increased vascular permeability remains to be proved. The question arises: "Why should there be increased local pulmonary permeability without any evidence of peripheral edema or increased peripheral vascular permeability?" The problem may be concerned with the parasympatheticomimetic factors controlling the pulmonary vasculature.

Numerous reports on cerebral complications may be found in the literature. Freed and Sachs, Wortis and others have described vascular changes associated with prolonged coma. In my study I attempted to correlate the performance test with the changes produced by the prolonged coma and the associated pulmonary

edema. Further studies at three month intervals will aid in determining the degree of recovery.

The Rorschach Method in State Hospital Practice. Dr. E. Louise Hamilton, Norristown, Pa. (by invitation).

The Rorschach method is a projective technic which is being used with increasing frequency in mental disease hospitals and in child guidance work. My associates and I have found it extremely useful in cases of difficult diagnosis in both the Norristown State Hospital and the child guidance clinics conducted by the hospital. The technic devised by Dr. Hermann Rorschach, a Swiss psychiatrist, consists of ten standard ink blots, five black and white and five colored.

The procedure consists of three parts: performance proper, inquiry and testing of limits. The scoring is not simple. There are fourteen scores for location, or the part of the blot used. There are also twenty-nine determinants, such as form, movement, color and texture. Content and popularity or originality of the answer are other types of scores. Interpretation of a Rorschach record is a highly skilled task and requires considerable training and experience. It is not possible to draw conclusions from any one factor unless they are confirmed by other factors.

Three cases are presented in which the Rorschach technic was especially helpful in the diagnosis and in the disposition of the patient. In 1 of these cases the patient was thought to be almost entirely recovered after a series of insulin treatments and prolonged coma with pulmonary edema. The Rorschach test showed that he had not recovered sufficiently to resume his former occupation. The results of the Babcock test agreed with those of the Rorschach method. Recommendations were made that he find a simpler type of occupation. Another case was that of a patient about the diagnosis of whose condition there was considerable disagreement. Traumatic psychosis, schizophrenia and manic-depressive psychosis were all considered. The Rorschach results did not reveal anything of a schizophrenic or organic nature and seemed to indicate that the patient had had an affective reaction. His condition was finally diagnosed as manic-depressive psychosis, and he later recovered and went home. Another case was that of an adolescent boy of 17 years whose condition had been diagnosed in another clinic as schizophrenia, but the Rorschach test seemed to indicate that he was not especially different from the average 17 year old boy who has not yet solved some of his sexual conflicts. Later, after a short period of treatment in the child guidance clinic, he found a job. According to recent reports, he is adjusting well in the Army.

Testosterone Therapy of Involutional Psychosis. Dr. E. F. Kerman, Norristown, Pa. (by invitation).

In this study, 12 male patients with involutional melancholia were treated with testosterone propionate. There are several reasons that this work was undertaken. First, conflicting reports have appeared concerning the value of testosterone in cases of involutional psychosis in males. Results in the various investigations range from 100 per cent recovery to no improvement at all. Second, the number of cases cited in the literature is small, and it was felt that further work would aid in the statistical evaluation of the efficacy of the drug. Third, the dose employed by other workers, usually 10 mg. three times weekly, has been questioned, the suggestion being given that 25 mg. is a more effective amount. The latter dose was employed in this study.

All of the males admitted to the Norristown State Hospital in the past five years whose condition had been diagnosed as involutional psychosis were considered for treatment. Of this group, there were 12 for whom the diagnosis was clear and whose symptoms had remained constant for a period sufficiently long that the likelihood of a spontaneous remission during the period of treatment was minimized. The ages of the selected patients at the onset of their illness ranged from 53 to 64 years. The duration of the psychosis varied from one and a half

to five years. Other treatments had been employed previously with 5 of the patients. Full courses of metrazol given to 2 of these 5 patients brought about no change. With 2 others convulsive shock therapy had been tried but had to be terminated because of cardiac decompensation resulting from treatment. In 1 patient narcosis had been induced with sodium amytal, with no improvement. Practically all of the men were poor risks for shock therapy because of their age or physical condition.

Testosterone propionate, in ampules containing 25 mg. in oil, was injected intramuscularly three times weekly for thirteen weeks. The patients were not told the nature of the treatment or its purpose. No effort at psychotherapy was made. The patients were then observed for two months and again given testosterone for seven more weeks. They were observed for two months after this. In all, this study covered a period of eight months, and each patient received a total of 1,500 mg. of testosterone propionate.

Of the 12 patients, 11 showed no improvement whatever either during or after treatment. Two of the 11 patients showed increased agitation during treatment, which subsided considerably afterward. One patient improved. He was 56 years old at the onset of his psychosis three years before. About a month after treatment was started, he began to take an interest in ward work. He continued to show improvement, and seven months after the beginning of testosterone therapy the staff of the hospital considered him well enough to grant the request of his family that he be allowed to return home, where he is at present.

The results, therefore, show 1 case of improvement among 12 patients. One cannot say whether the improvement in the 1 patient was due in any measure to the testosterone or whether it was coincident with treatment. Since the course of the majority of the patients was unaltered by the substance, it seems that one can state with reasonable assurance that testosterone propionate appears to have little or no effect in the treatment of involutional melancholia in the male.

Psychosis Associated with Progressive Muscular Dystrophy. DR. B. H. GOTTESFELD and DR. H. H. HERSKOVITZ, Norristown, Pa.

The case here reported concerns the development of dementia praecox in a single white man aged 24 who suffered from progressive muscular dystrophy. He has a brother who is not psychotic, but has progressive dystrophy, and a twin sister who has escaped both diseases.

The family history is without significance. The mother died when the patient and his twin were born. The twins were raised by the maternal grandparents, while the brother was brought up by the paternal grandparents. After his wife's death the father took little interest in the children. He was said to have been ashamed of his sons because they were crippled. The patient was described as kind, gentle and obedient. He liked to read poetry, philosophy and books on etiquette. In both brothers the onset of muscular dystrophy occurred at the age of 8 years, and weakness progressed gradually. Our patient was fearful of becoming dependent on others and did everything he could to better himself. Although working under a great handicap, he graduated from high school. He took a business course, with the hope of later supporting himself. Home conditions were rather poor in that the people with whom he lived were unsympathetic. He considered them vulgar and disliked their profanity. The patient's brother was always shielded by his grandparents. He took little interest in school. His grandparents did not permit visitors because they did not want the boys "gawked at." Long before the patient consented to wear crutches his brother was spending all of his time in a wheel chair. The patient's psychosis occurred suddenly. He expressed the belief that he was poisoned; he heard voices of a condemnatory nature and was loud, destructive and assaultive.

The pertinent literature is reviewed. The difference in the prepsychotic personality of the patient and that of his brother and the possible reasons for the development of a psychosis in the patient are discussed.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

H. HOUSTON MERRITT, M.D., *Presiding*

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Potentials of Rapid Frequency in the Human Electroencephalogram.

DR. KNOX H. FINLEY.

Gibbs in 1937 described the range of frequencies of the bioelectric potentials of the brain as the "cortical frequency spectrum." This spectrum may be divided into three bands: (1) slow, 1 to 8 cycle per second waves; (2) medium, 8 to 12 cycle per second waves, and (3) rapid, 12 to 40 or more cycle per second waves. This study is concerned with those cycles of rapid frequency which have an amplitude of 25 microvolts or more. Most of these cycles are within the 18 to 30 per second range of the rapid frequency band.

Although these high voltage, rapid cycles occurred in a small percentage of electroencephalographic tracings from normal control subjects (less than 5 per cent), they appeared in a significantly higher percentage of tracings from over 4,500 persons representing a variety of neuropsychiatric disorders. Three inferences are to be made from this study: (1) Rapid frequency patterns are widely distributed throughout the neuropsychiatric disorders; (2) similar types of rapid frequency patterns are encountered in a variety of clinical conditions, and (3) various types of rapid frequency patterns are to be found among patients with the same clinical condition.

Gibbs, in his studies on epilepsy, was the first to call attention to a certain type of rapid activity. Because he was impressed by its frequent occurrence in cases of grand mal epilepsy he termed such activity "grand mal activity." In my experience similar activity is encountered with a variety of clinical conditions, and even more often with neurosyphilis and affective psychoses than with grand mal epilepsy.

DISCUSSION

DR. FREDERIC A. GIBBS: Some of Dr. Finley's remarks were aimed so directly at me that I can hardly escape the necessity of replying. The tremendous number of cases that he has studied entitles him to speak with authority not only on the psychoses but on epilepsy.

My associates and I have good precedence in electroencephalography for the use of clinical and electrical terms interchangeably. The clinician is interested not in a neurophysiologic interpretation but in clinical correlations. We find it convenient to abbreviate the statement "3 per second wave and spike activity of the type most commonly seen during petit mal seizures" to "petit mal type of disorder," and similarly for grand mal and psychomotor seizures. Dr. Finley has said that what is called grand mal activity is not seen most commonly with grand mal seizures. It is possible that we have used this term too loosely and have misled him. We have always made a distinction between more or less steady fast activity and true grand mal activity. We have tried to reserve the term "grand mal" for a discharge of the type which is seen at the time of a grand mal seizure, just as we have reserved the term "petit mal" and "psychomotor" for the type of activity seen during petit mal and psychomotor seizures. It is true that grand mal discharges are rare in interseizure records, but we have never encountered a grand mal discharge in the tracings of more than 3,000 normal control subjects or in those of more than 4,000 patients with neuropsychiatric disorders unassociated with epilepsy. The latter group represents every type of disorder which Dr. Finley has studied. All recognize that the electrical activity of the cortex as it appears in the electroencephalogram is exceedingly complicated. There are many ways in which to regard it. If it is looked at in our way, certain definite correlations can be found between epilepsy and special types of seizure patterns. I cannot believe that Dr. Finley wishes to deny these correlations. They are as

real as anything in electroencephalography and as good as many of the most important correlations in clinical neurology. If any one wishes to use different words, "rapid activity" instead of "fast activity," "spike and wave" instead of "wave and spike" or "abnormal waves" instead of "dysrhythmia," that is immaterial, but the facts remain; they are as we have stated them, and they can be seen by any one who has requisite powers of discrimination.

DR. ROBERT S. SCHWAB: Dr. Finley's paper is important because it emphasizes a band of frequency often disregarded in the localization of tumors and in the study of cerebral disorders. My first contact with fast frequencies came in a case in which from a localized area of 3 to 4 cm. there was a continuous discharge with a frequency of about 18 to 26 cycles. One of my associates suggested that this looked like a muscle discharge, though it was above any muscle. It was not present on the other side. The patient had jacksonian convulsions, and operation, which was eventually performed at the Massachusetts General Hospital, revealed an infiltrating glioma. We often wheel the portable electroencephalograph into the operating room for direct recording from the exposed brain. In this case the same fast frequency was picked up from the tumor, but was not picked up 5 cm. away from the infiltrating tumor in normal cerebral cortex. Therefore we were sure that this was actually a cerebral discharge. Dr. Finley did not emphasize that this fast frequency looks like that of muscle. In the particular case I cited we eliminated the possibility of this fast frequency's being from muscle. Sometime later Dr. Madelaine Brown and I, in examining a group of patients with Ménière's disease, encountered a frequency which resembled that of muscle. Our final conclusion was that there is, in patients with intense vertigo of Ménière's type, a fast frequency discharge from the cortex that looks something like a muscle potential. But I do not think one can be certain that there is not some muscle discharge in these tense patients when they are suffering from attacks of vertigo. Further evidence that would verify the assumption that these discharges are really cerebral and related to an abnormal cortex I observed during operation on 4 patients with Parkinson's disease. In all 4 patients I noted increased voltage and increased fast activity from the cortex in a region where there was no muscle within 6 cm. of the electrodes. At the time of the first observation of this fast frequency, I suggested to the neurosurgeon that this was an abnormal discharge and that he had better use a weak current for stimulation. This he did not do, and in two or three minutes the patient had a generalized seizure on the operating table. This happened a second time with another patient who showed high frequency waves with cortical stimulation; so I am convinced and I agree with Dr. Finley that such fast frequencies do occur in the cortex. I have seen them on six occasions in the operating room. One must be careful, however to eliminate muscle frequencies, which parallel this band closely.

DR. FREDERIC A. GIBBS: I should like to spare Dr. Finley from having to defend himself against the imputation that he may have confused fast activity of cortical origin and muscle potentials. A beginner might make such a mistake, but any one with a good instrument and sufficient experience will be able to distinguish certain types of fast activity which are not that of muscle. I am sure that Dr. Finley can do this and that in what he has said about rapid activity he referred to a type of activity which is clearly distinguishable from muscle activity.

DR. WILLIAM G. LENNOX: Dr. Finley deprecated the practice of not using a sufficiently large "gain" so that abnormal waves are clearly discernible. I should criticize his slides for the same reason. With so many tracings on a single lantern slide, each tracing is so small that we of the audience are unable to judge whether his rapid waves are from brain or from muscle. Also, he did not show samples of rapid activity from his normal group.

DR. KNOX FINLEY: I disagree with Dr. Gibbs's statement that the clinician is not greatly interested in neurophysiologic interpretations. It is this very interest that makes the clinician so critical of Dr. Gibbs in his use of clinical terms

in interpreting his neurophysiologic data. The clinician is aware of the limitations of these clinical terms and has reason to be skeptical. Dr. Gibbs has stated that perhaps he has used the term "grand mal activity" too loosely, and that it should be limited to a discharge of the type which is seen at the time of a grand mal seizure. In my experience "grand mal activity" varies even during a grand mal seizure. Furthermore, activity of the type occurring during grand mal attacks is by no means limited to grand mal epilepsy, but, as I have shown, is associated with other neuropsychiatric disorders. There must of course exist some correlation between epilepsy and special types of seizure patterns. From my own studies I am not clear as to what these correlations are; furthermore, I am unable to confirm the special correlations which Dr. Gibbs finds, or at least implies.

Dr. Schwab has raised the question of one's confusing rapid activity with muscle artefact. The two may be confused if one does not use the necessary precautions. There are several ways of ruling out muscle as the source of the rapid activity, which I have described this evening. For example, these rapid frequency cycles of cortical origin are often better brought out by the bipolar technic, in which the electrodes are more removed from the source of muscle, than by the monopolar technic, in which the indifferent electrode lies near muscle tissue. In cases of neurosyphilis one sees these rapid cycles disappear with antisyphilitic treatment and clinical improvement. Furthermore, rapid activity of cortical origin is sometimes seen in the early stages of physiologic sleep, when the subject is well relaxed.

Dr. Lennox criticizes the amount of gain used in the samples illustrated in the lantern slides. Most of the samples shown were amplified two or three stages, which I believe is in keeping with the amount of gain Dr. Gibbs and Dr. Lennox often use in their laboratory. My lantern slides were not made up to establish that these rapid waves were from the brain rather than from muscle. As Dr. Gibbs has already stated, with a little experience and care one need not confuse a muscle artefact with rapid potentials. The rapid patterns which occurred in the tracings of a small percentage of my normal group were sufficiently similar to those illustrated in the lantern slides that, in the time allotted, I did not feel justified in duplicating them.

The Kenny Method of Treatment of Infantile Paralysis. DR. ARTHUR L. WATKINS.

The National Foundation for Infantile Paralysis has recently sponsored in Minneapolis a course for physicians to demonstrate the Kenny method of treatment and to present for evaluation the original cases in which the treatment was employed. My conclusions are based on evidence presented in this course.

The traditional treatment of poliomyelitis, although not standardized, will be outlined briefly for comparison. It is generally believed that flaccid paralysis develops from destruction of anterior horn cells, but in some instances certain groups of muscles are less affected and tend to cause deformities by imbalance. Splints are therefore applied to prevent this and to rest the affected muscles. When muscle tenderness has disappeared, active reeducation of weak muscles is started, the splints remaining on between treatments. There is great variation, however, in the time of starting motion and in the use of local heat and hydrotherapy.

The Kenny method of treatment is based on a different concept of the symptoms and the factors which lead to the development of deformities. Miss Kenny recognizes that there will be a certain variable percentage of patients with residual flaccid paralysis of one or more extremities. This is a result of complete destruction of anterior horn cells, for which no cure is known, nor does she claim any. Miss Kenny's treatment is directed toward another condition which she calls muscle "spasm." This symptom is thought to be of the utmost importance, for if it is not treated early, contracture, fibrosis, atrophy and loss of function will result. This so-called spasm consists in pain, tenderness on

pressure, constant hyperirritability, particularly on stretching, and in some cases visible fasciculation. After several weeks muscles which have been thus affected and not treated properly will exhibit contracture, fibrosis and atrophy. Kenny's term "spasm" refers in a general way to these conditions and is misleading if interpreted according to general usage.

Miss Kenny has further observed that in the majority of cases the posterior muscles of the neck, trunk and lower extremities are more affected by "spasm" than the anterior muscles with antagonistic action. She believes that if treatment is carried out in the traditional manner the antagonists of the muscles with "spasm" become lengthened and atrophied from disuse and that finally power of voluntary contraction is lost. She designates such a functionally paralyzed muscle as "alienated." She also speaks of it as "nonparalytic," which means that if the "spasm" of the antagonist is released and the muscle is allowed to regain its proper resting length, it may be made to function by proper stimulation and reeducation. She has learned to distinguish a truly paralyzed muscle from an "alienated" one by passively stretching the muscle a few times within a small range of motion; then, by careful observation, a functionally paralyzed muscle will be seen to become tense, so that its tendon will stand out beneath the skin. One might explain this by the assumption that the myostatic stretch reflex had thus been elicited.

A third factor leading to muscular dysfunction Miss Kenny has called "incoordination." This consists in the substitution of accessory muscles, or even antagonists, for the proper prime movers of a joint. Individual muscles also are said to contract improperly in sections rather than through their full length; again, this is spoken of as "incoordination." This phenomenon, I believe, is generally recognized to occur whenever there is attempted motion with partially paralyzed muscles around a joint and also when the joint is immobilized.

The Kenny method of treatment aims to eliminate or correct these three factors leading to deformity and impaired movement. The muscle "spasm" must be treated as soon as the diagnosis is made. A delay of as little as three or four weeks may seriously compromise the results. Treatment consists in the application of hot packs of a measured size to fit muscles without immobilization of the joints. These woolen packs are immersed in boiling water, wrung out twice through a tight wringer at the bedside and applied quickly to the involved part. The pack is then rapidly covered with oiled silk and a layer of dry flannel. The packs are changed every fifteen minutes if spasm is acute; otherwise, every two hours for a twelve hour period each day. Spasm is usually relieved within a week by such treatment, but packing is continued for weeks or months if the muscle exhibits contracture or shortening. Although the original temperature of the pack is high, there is rather rapid cooling, and at the end of two hours there is probably a tendency for the body to heat the pack. This is in reality, then, a type of contrast therapy.

No active or passive movements which cause any spasm or pain are allowed. When the spasm is relieved, passive motions only are started while the packs are still in use, and the muscles are said to be "stimulated" by this. One might interpret this physiologically as the setting up of a barrage of proprioceptive impulses to facilitate the motor pathway and the proper pattern of response. Active motion, or muscle reeducation, begins only when spasm has been relieved. This may be within a week in some cases, while in others some muscles may exhibit residual spasm which requires hot packs for months.

Miss Kenny's system of muscle reeducation emphasizes the isolated action of certain important muscles for each movement of a joint. The patient is taught exquisite control of agonists and antagonists so that smooth rhythmic motions are obtained. There is no effort to strengthen individual muscles by resistive exercises, but the purpose is to increase strength by repeated coordinated movements. All the patients I saw there were beautifully trained in the performance of these motions and were flexible to a degree rarely seen in average normal persons.

The most convincing evidence available at present in favor of the theory that muscle spasm if untreated leads to contracture deformities is obtained by comparing the patients treated by the Kenny method with others in the same epidemic who were treated early by immobilization without packs. Whereas in the first group there was complete freedom of motion in all joints through a normal range, in the latter group a mild or severe degree of stiffness and contracture could be demonstrated, particularly of the posterior muscles of the back and the lower extremities.

The nature of muscle "spasm" is unknown, but several possibilities will be investigated in the future. In a recent case my associates and I have observed abnormal electrical activity as judged by the electromyographic tracing from an involved muscle. In another case of long standing, an apparently paralyzed muscle responded well to faradic stimulation, an observation suggesting that functional paralysis may occur in this disease.

It is extremely difficult to evaluate statistically the results of treatment of different groups of patients with poliomyelitis because of the variability in the extent of paralysis which is to be expected. Eighty-four patients in the early stage have been treated in Minneapolis by the Kenny method. Among these patients there were residual paralyses in 10 lower and in 2 upper extremities. Although all patients showed involvement of muscles of the neck and back and the hamstring muscles, in no instance was there residual involvement of the trunk. The most striking feature observed in these patients was the ease and coordination of movement and the remarkable suppleness. None of the familiar contracture deformities were seen, and the condition of the skin, subcutaneous tissues, muscles and joints in the paralyzed extremities was better than is usually seen as judged by inspection and palpation. Although no splints or supports were used while "spasm" was present, they were not objected to after the period of recovery. No deformities resulting from this lack of immobilization were observed. The comfort and morale of patients under treatment were impressive.

In summary, the following conclusions are stated:

1. In acute poliomyelitis "spasm" of affected muscles is a condition of undetermined cause, which if untreated leads to contracture deformities, functional paralysis of antagonistic muscles and dysfunction of accessory muscles.

2. Muscle "spasm" is relieved by the application of hot packs as described if treatment is started within the first week or two of the illness.

3. Functional paralyses are prevented by elimination of spasm of antagonists and by stimulation of proprioceptive impulses through passive movements.

4. Smooth, coordinated movements are developed by a system of muscle reeducation stressing isolated muscle action.

5. Contracture deformities have been eliminated without the use of splints.

6. Functional results are equal or superior to any known method of treatment, although residual flaccid paralysis is not eliminated.

7. Similar results have been obtained by many different users of this method of treatment.

DISCUSSION

DR. FRANK R. OBER: I had heard a great deal, both pro and con, about Miss Kenny's method of treating infantile paralysis. Last autumn, I made a visit to Minneapolis and spent a day with her at the clinics, and had a very interesting time.

In 1915 Dr. Lovett and I began the use of hot packs and hot baths in the early treatment of infantile paralysis, but of course most of our patients did not come to us until several weeks after the quarantine period was over. We found that with the use of hot packs and baths the patients with deep sensitiveness were made more comfortable; we also noticed that they could move their legs in a hot bath when it was impossible to do so on a bed.

Of course Miss Kenny's treatment is an all day affair, in which she bakes the legs in hot fomentations by a special technic, and there is no question that the

sensitiveness and muscle spasm disappear much more rapidly than with the standard therapy. She states that contractures and spasm and limited motion in joints occur as a result of prolonged immobilization. I have seen these phenomena many times even when there was not much paralysis present.

Personally, I have adopted the practice of applying wire splints to the extremities when they are in the position of comfort and of using the hot packs or hot baths three times a day, and I have found that the flexed extremities will relax and gradually straighten out. The wire splints have the advantage over plaster casts in that they can be bent to follow the line of deformity as the leg improves.

There is one element in poliomyelitis that is confusing; that is, tenderness and pain in the nonparalyzed extremity may be even greater than in the paralyzed extremity, and sometimes it takes a long time for the nonparalyzed extremity to be relieved of the pain. It has been our experience that deep massage always increases the tenderness and deformity, the latter being due to the spasm of the muscles.

Patients with poliomyelitis appear to be perfectly comfortable in bed until some one tries to do bed nursing; then it is found that the legs, the arms or the back is sensitive. Sensitiveness may be elicited by straight leg-raising, muscle squeezing, dorsiflexing the calf or putting any of the flexor muscles on the stretch. If the leg is allowed to assume a bad position, contractures may develop which will be difficult to straighten out.

If one is to use the Kenny treatment, it must be carried out thoroughly; otherwise, one must prevent deformities by other methods which are known and fairly well standardized. In Sister Kenny's cases, however, there does not seem to be the atrophy which occurs from prolonged splinting. I found in her cases that the skin was in excellent condition, with apparently normal color and normal circulation. If immobilization is to be given up entirely, the nursing care must be of the best.

I believe that the early application of heat as advocated by Sister Kenny is a distinct advantage in the treatment of infantile paralysis and that with this method the deep pain and spasm disappear much more readily than with the older methods of prolonged immobilization and lying in bed.

DR. D. E. DENNY-BROWN: I agree entirely with Dr. Ober's impression. Miss Kenny's treatment was the subject of two committee reports in Australia in 1936. It was the impression of those committees that her success was due to the intensity rather than to the nature of her system. Perhaps an orthodox method, used as intensively, would have been as good. In 1937 she went to England and was given three wards, a treatment clinic, all the apparatus she wished and five whole time masseuses. The original plan was to review the situation after three months, but the period was extended to a year. At the end of that year a combined committee of neurologists and orthopedists made a report. At that time she had not evolved the present rationalization of her method. Spasm was not then an important factor, nor was "alienation." At that time, too, she claimed that if her treatment was started sufficiently early, a complete "cure," as she termed it, could be obtained. The validity of that assertion was denied by the committee, who found that her claim of effecting a complete cure was not substantiated. She has since dropped this claim and recognizes that persistent flaccid paralysis is sometimes encountered. It was found that her methods of hydrotherapy were valuable and did no harm, but the committees were not convinced that very early application of them, or of passive or attempted active movements, was essential. My own histologic experience in observing torn muscle fibers in the early stages of the disease certainly gives me great respect for recently paralyzed muscle. It was found by the committee that splints can often be dispensed with in the early stages, but are sometimes valuable and essential. It was further felt that at that time Miss Kenny had begged the question of subsequent deformity and was not capable of dealing with the mechanical situation resulting

from persistent paralysis. I should like to ask what happens now with respect to the late stage of such paralysis, for Miss Kenny has modified her views considerably since then.

Unfortunately, Miss Kenny would have none of any method that attempted to combine other, most useful measures with her therapy, and so to her the world was divided into those who would accept her treatment in every small detail and those who would not. Most workers prefer not to be driven to one extreme in every detail or to apply a rigid routine in every case. Dr. Ober expressed it perfectly when he said there was no such thing as an orthodox method.

I am intrigued by the question of "spasm," or "spasticity," and I should like to ask whether by the term Miss Kenny refers to rigidity of the neck and to resistance to movement in the neck and shoulders, particularly in the early stages of paralysis. Many investigators have noted that long after the spinal fluid has returned to normal, or has shown only an increase in protein, there is often persistent rigidity of the neck. I myself had attributed this symptom to the fact that the spinal cord was still inflamed. Might this condition of "spasm," therefore, be central in the sense that tension on meningeal attachments causes "spasm," without any reference to lesions in the muscles? In that case, would not the hot packs and heat be better applied to the spine than to the affected muscle?

Dr. James B. Ayer: I agree with Dr. Ober that there must be value in the Kenny treatment. At the Massachusetts General Hospital, my associates and I felt strongly enough about this treatment to send Dr. Watkins to Minneapolis, where he spent a week. He has come back enthusiastic. If an epidemic of poliomyelitis occurs, we plan at the hospital to place certain patients under this treatment and to study them with reference to certain laboratory tests which are not being used at Minneapolis, particularly electromyographic studies. I was especially interested in a remark made by Dr. Smith-Petersen, who, when asked his opinion of this treatment, said: "After all, orthopedists do not all have set methods of treating this disease. Many do use fomentations now and carry out active muscle training in the early stages." In any case, Sister Kenny has emphasized active therapy in the early stages of paralysis, and the results obtained justify reevaluation of the method by persons directly concerned with the treatment of poliomyelitis.

Dr. Robert Schwab: Does Dr. Watkins know of any application of this therapy to disease of the anterior horn cells and muscle atrophy? I wonder whether this method of heat and massage would not be a sensible therapeutic venture in management of fibrillation, which so far has not responded to use of vitamins or other treatment.

Dr. H. Houston Merritt: How expensive is this treatment, and how much nursing care is needed?

Dr. Arthur L. Watkins: I think that Dr. Ober and the other discussers are entirely right in emphasizing that there is no one traditional treatment, and Dr. Ober has long pointed out the disadvantage of using massage when one is not careful of the tender muscles. Many people overlook the spasm in muscles. Miss Kenny has changed a great deal in her concepts. They notice it in Minneapolis as time goes on. She learns from the physicians who go out there; so her method is not any one set type of treatment. She states she never saw the bad cases in Australia that she has seen in Minneapolis, and she admits that she does have cases of residual paralysis. While I was there she said, "This person should have some braces and supports and probably some stabilization operations on his feet." She is still rather ritualistic, as in the pack treatment, and I think many observers are not particularly impressed. It seems as though something easier and more effective should be developed. She makes a point of distinguishing between rigidity of the neck and back due to meningeal infection and that occurring in poliomyelitis. She was not able to convince me exactly, and I am still not clear as to what the difference may be. I think the meningeal irritation may be an explanation to some extent, but the mechanism is vague. She does treat the region of the neck and spinal cord.

I do not know whether this treatment has been applied to progressive muscular atrophy. Miss Kenny does not employ massage. The use of heat is directed toward the muscle, although she has applied it in Australia in cases of infantile cerebral palsy for relief of spasticity. As for its effect on fibrillation, that, also, has not been studied.

In Warm Springs, Ga., they have adopted the policy of using ward maids for applying packs, which they can do at a minimum cost. If this were done by the nursing personnel the expense would amount to a great deal.

Toxoplasmic Encephalitis: Clinical Experience. DR. BRONSON CROTHERS.

Toxoplasmic infection as a cause of cerebral and ocular lesions in children was unknown until a series of papers by Dr. Abner Wolf and his associates, in New York in 1937 and thereafter, and by Dr. A. B. Sabin and his associates, in Cincinnati, proved that a significant number of cases existed. Other important papers by Pinkerton and Weinman and Pinkerton and Henderson indicate that adults can also acquire damaging or fatal lesions.

The wide geographic range of the parasite and its many animal hosts make it likely that the distribution of cases of the disease in man is almost universal. Certainly, the cases reported here come from widely separated places, as is usual in hospital and private practice.

Pathologic studies on newborn infants have demonstrated the organism in the eye and in the brain.

The evidence that intrauterine infection takes place is increasingly convincing. The final proof, which could be obtained by identifying toxoplasmas in the placenta, is still absent, but the results of tests of the blood and other observations make the hypothesis defensible.

The evidence certainly suggests that the organism may live for many years and that it carries a serious threat to future children of a mother who has had one infected child. On the other hand, there is no evidence that the infection does not completely die out in most cases. As far as I know there is no report that viable organisms are found in later offspring, although clinical evidence suggests that they may lurk in tissues for years.

The first reports, of course, dealt with the cases of severely damaged infants. In these children hydrocephalus was the rule. It is now evident that certain persons survive without important handicap, even if the infection involves both the brain and the eyes. Furthermore, it is probable that a fair number of children suffer cerebral damage without calcification, and it seems certain that the eyes alone suffer in others. Available evidence also indicates that infection may occur without producing any symptoms or signs at all. In general, it seems clear that calcification may be present without altering the brain bulk or distorting the ventricles in any way.

The development of a method for the recognition of the disease in the laboratory is due to Sabin and Olinsky (*Science* **85**:336, 1937). The procedure involves intradermal injection into a rabbit of infected mouse brain mixed with varying quantities of the blood of the suspected person. A high degree of protection is afforded by the presence of the blood of a person who has been infected. Readings are taken after a few days.

The obvious suggestion that certain rabbits are immune and therefore will produce false positive reactions has been followed up, and all objections which occur to me have been met. Ample controls have been used.

Sabin reported that tests on a considerable sample of persons with no obvious infection gave positive results in about 10 per cent. He suggested that these persons might well have subclinical toxoplasmic infection. Certainly the investigation of several families indicates that this hypothesis is reasonable.

In this paper a small series of cases is presented in which a clinical diagnosis of toxoplasmic infection was supported by serologic evidence. All the children were seen at the Children's or at the Infants' Hospital, and none of them was

referred here as having a probable or proved case of the disease. The disease was called to the attention of the staff of the Children's Hospital under the following circumstances:

The first case was that of an intelligent, competent girl of 12 years with choreoretinitis and calcification. She had had a single severe convulsion. Tests for the presence of the organism in the blood of various members of the family made in our laboratory gave the following results: father, negative; mother positive; sister, doubtful; sister, doubtful, and patient, strongly positive.

The second case was that of a 7½ month old girl who had mild hydrocephalus and microphthalmos with calcification. Results of tests of the blood of all members of the family for toxoplasma were as follows: father, negative; mother, positive; brother, positive, and brother, positive.

The third case, seen first in 1929, was that of a girl with convulsions and calcification without choreoretinitis. The tests on her blood and that of her mother have not been completed.

The fourth case was that of a boy with convulsions, choreoretinitis and calcification.

The fifth case was that of a boy, a younger brother of the fourth patient. He had choreoretinitis, hemiplegia and calcification with mental retardation. The results of testing the blood of this family were as follows: mother, positive; brother (case 4), positive; normal brother, moderately positive; brother (case 5), positive; sister, negative, and sister, negative.

The sixth case was that of a girl with choreoretinitis, calcification and convulsions.

The seventh case was that of the younger brother of the preceding patient. He had similar symptoms; the mother had calcification without choreoretinitis, and another sister had calcification but no ocular or mental symptoms. The blood of the mother and these 3 children was reported to be positive for the organism.

The eighth case was that of a boy of 10 years and 7 months who had convulsive attacks, choreoretinitis and calcification. Roentgenograms of the skull of the father, the mother and the sibling were without significance. Tests of his blood and that of his mother gave positive reactions for Toxoplasma.

The ninth case was that of a boy of 4 years and 9 months with mental defect, choreoretinitis and calcification. The mother and a sibling showed no choreoretinitis, but studies of their blood were not possible. The blood of this child was reported to be positive for Toxoplasma.

In the course of this investigation, which was largely an attempt to remember instances of the disease, I have collected 10 cases in which the clinical requirements were fulfilled and serologic reactions were positive. In addition, 8 members of the families represented reacted positively to serologic tests but did not present clinical evidence of the disease.

In 3 other presumptive cases serologic tests are now being made, and 2 others which are clinically typical are being sought for but efficient contact has not yet been established.

DISCUSSION

Dr. David H. Weinman: Dr. Crothers has described the clinical and roentgenologic features of infantile toxoplasmosis. Toxoplasma in the fresh state is curved and somewhat resembles a bow, hence its name. It is a crescent body with tapering ends, measures about 6 by 1.5 microns and shows only one constant internal structure, the nucleus. The parasites may be either intracytoplasmic or extracellular. When intracytoplasmic they are massed together and often appear smaller and ovoid. Intracellular collections vary considerably in size, may reach 50 microns in length and are then easily visible with low magnification. Reproduction takes place by binary longitudinal fission. At one time multiple division (schizogony) was also thought to occur, but this observation has not been confirmed and was apparently due to misinterpretation of the intracellular masses.

In addition to its presence in man, Toxoplasma has been reported in a great variety of animals, including, and this is suggestive, those frequently in contact

with man, that is, domesticated or semidomesticated animals or pets, such as dogs, rabbits, mice, rats and birds.

Are the infections in man and in animals caused by one or more species of Toxoplasma? All the evidence thus far produced indicates that there is only one species. This conclusion has been reached since (1) toxoplasmas originating from any one animal are infective for many generically different hosts, and (2) Toxoplasmas of different origins cross immunize against each other.

Since Toxoplasma has such a wide distribution among animals, it is not surprising that it is equally widely distributed geographically, now having been reported from all continents. Cases of human infection have now been reported from Czechoslovakia, Netherlands and Brazil and, in the United States, from Boston, New York, Chicago and St. Louis.

Concerning transmission information is not yet complete. It has been proved that congenital transmission takes place both in man and in animals. It is likewise proved that carnivorous animals may acquire the infection by ingestion. These are the only two methods established and do not appear adequate to explain all the cases: notably, those of adult infection in man and of toxoplasmosis in herbivorous animals. It has been suggested that arthropods, notably ticks, may transmit the disease, but experimental support for this view has thus far not been obtained.

The diagnosis may be suggested by the clinical data which Dr. Crothers has so ably presented in connection with the disease in infants. In adults the symptoms appear to be less well defined; neurologic manifestations are not conspicuous, and abnormalities of the heart, lungs and liver may furnish the outstanding signs.

Of the laboratory procedures which are available for diagnosis, direct demonstration of the parasite has an unusually high value. Toxoplasmas have been seen in sediment from the spinal fluid and in the papules which sometimes occur as a cutaneous manifestation of the disease; in case of the latter biopsy may be considered. At autopsy the lesions are usually conspicuous, and parasites are seen within or at the periphery of these cutaneous areas. In the congenital type the tissues which are most often invaded are the brain and eyes, and in the noninfantile type, the lungs, heart and liver.

Indirect means of demonstration involve animal inoculation and serologic tests. The intracerebral inoculation of mice is the preferred method. Blood, spinal fluid, ground tissue—all may produce infection, which results in death usually in one to three weeks, but the animals should not be discarded for two months. One inadequacy of this method is the frequency of spontaneous infection in mice. Therefore it is advisable to use numerous animals—at least six, which are chosen if possible from different litters. Guinea pigs and rabbits may also be used, subject to the same caution, and may be more susceptible to certain strains than mice.

Embryonated chicken eggs can also be infected. For diagnosis they have one certain advantage; i. e., they are not known to have spontaneous toxoplasmosis. They are, however, less sensitive to small doses of the infecting organism than are mice when inoculated as described in the preceding paragraph.

Several serologic tests have been described, but only one has been used in connection with human cases. This is a protection test in which two sets of progressive dilutions of the living toxoplasma material are prepared. One set is mixed with the serum to be tested; equal amounts of normal serum or of Tyrode's solution are added to the other set, which serves as the control. A single rabbit is inoculated intracutaneously with both sets of infective material. Results are read at the end of ten to twelve days. The control inoculations result in areas of necrosis, which vary roughly with the infective dose inoculated; protection is manifested by a smaller area of necrosis as compared with that for an equal infective control dose. The value of this reaction is being established. It is probable that a negative result will prove to be of little value in excluding toxoplasmosis, whereas a positive reaction is significant, although the degree of specificity is not yet known.

The pathologic lesions are conspicuous and important. They consist of multiple foci of necrosis of variable extent infiltrated with polymorphonuclear and mono-

nuclear leukocytes and plasma cells. Lesions of this type are most frequent in the central nervous system, meninges and eye or in the heart, liver and lung. Some of the lesions of the brain become calcified and are then visible ante mortem with roentgen rays.

Difficulties in the differential diagnosis of the parasite in the tissues arise with five groups of parasites: Trypanosoma cruzi, Leishmania, Histoplasma, Sarcocystis and Encephalitozoon. The distinction may usually be made on morphologic grounds alone, although cultures and animal inoculations furnish additional criteria.

DR. BRONSON CROTHERS: The disease has, of course, been described by Dr. Wolf and Dr. Sabin and their colleagues. The clinical material I report is chiefly interesting because the children are older than those in many reported cases. It has been my experience that the suggestion of toxoplasmosis should arise when the ophthalmologist is puzzled by the presence of choreoretinitis. If calcification of the brain occurs in addition the presumption is strong. Treatment after cerebral or ocular invasion is presumably futile, but the fact that the mother may react positively suggests that efforts at treatment, in the attempt to prevent infection of future children, should be made.

DR. CLEMENS E. BENDA, Wrentham, Mass.: When I saw Dr. Crothers' roentgenograms and heard his discussion of the calcification, I thought of tuberous sclerosis. Of course the two diseases are entirely different, but it struck me as significant that Dr. Crothers described lesions in the heart, the liver and the lungs, together with the calcifications in the brain. In cases which have been considered instances of tuberous sclerosis lesions in the heart and liver have frequently been shown—especially the rhabdomyoma of the heart is frequently associated with tuberous sclerosis. I wonder whether some of the cases in which the diagnosis has previously been tuberous sclerosis were not really cases of toxoplasmosis. I should like to ask whether in Dr. Crothers' cases the skin was sometimes affected, and what kind of cutaneous changes were observed.

DR. BRONSON CROTHERS: I think Dr. Weinman has found definite evidence at times of lesions of the skin.

DR. DAVID WEINMAN: Yes. I have not as yet studied the lesions in tuberous sclerosis.

DR. PAUL I. YAKOVLEV, Waverley, Mass.: How were the cutaneous lesions distributed?

DR. DAVID H. WEINMAN: They were disseminated in the 2 cases I recall. In 1 case small pinkish, very firm papules were observed. In another case the lesions were reddish pink and suggested typhus. Also, they were not distributed in any particular region of the body

DR. PAUL I. YAKOVLEV, Waverley, Mass.: It is evident that tuberous sclerosis and cerebromeningeal angiomatosis, or Weber-Sturge disease, on one hand, and toxoplasmic encephalitis, on the other, are entirely different conditions. Nevertheless, one may readily see how easily the confusion may arise, and it is quite likely that the diseases will be confused at times. Indeed, clinical features, such as the mental deficiency, the epileptic fits, the occurrence in siblings and the strikingly similar appearance of intracerebral calcifications in roentgenograms, are common to these conditions. Histopathologically, the confusion is hardly possible. Indeed, as has been seen today, the toxoplasmic encephalitis is an infectious, inflammatory and degenerative disease in which a pathogenic agent is often demonstrable. Nothing of the sort is ever seen in cases of tuberous sclerosis or cerebromeningeal angiomatosis. The difference between these two "neoplastic malformations," which they essentially are, and the toxoplasmic encephalitis is of about the same magnitude as the difference between a neoplasm or malformation and a necrotizing inflammation. There are clinical differences, too, that should permit differentiation in most cases. First, the calcification in tuberous sclerosis and in cerebromeningeal angiomatosis does not seem ever to occur before puberty; second, these two conditions are system diseases which involve not only the nervous system but, in a characteristic fashion, the skin and

other structures of ectodermal derivation, such as the retina, the nails and the visceral ganglia and plexus. In the presence of such systemic generalization of the neoplastic malformations, the confusion with toxoplasmic encephalitis should not be possible. I must admit, however, that in cases without neurocutaneous manifestations, the differentiation between these malformations and the toxoplasmic encephalitis may present considerable difficulty.

DR. ALEXANDRA ADLER: What is the character of the spinal fluid in toxoplasmosis?

DR. BRONSON CROTHERS: I have had only 1 case in the acute stage, that of a baby, and in that the disease was, I should think, of two or three months' duration. There was no sign of actual activity at that time, and nothing abnormal was noted in the spinal fluid. In some of Wolf's cases there have been a high protein content and indiscriminate signs of inflammation of the eyes. Dr. Wolf says the organism was seen in the sediment in 1 clinical case.

Book Reviews

Unconsciousness. By James Grier Miller. Price $3. Pp. 329. New York: John Wiley & Sons, 1942.

The author is to be complimented especially on two things—he has written the book in good style so that it is readable and pleasing; second, he meticulously defines his terms and never lets the reader forget the sinfulness of ambiguity. In this one senses the influence of Lawrence Henderson, who struggled so valiantly to bring the exactness of chemistry to the aid of sociology.

There are two objectives in this monograph. The first is to show that much harm has come from the divorce of academic and laboratory psychology from clinical psychiatry. The second is the discussion of unconsciousness.

"Consciousness is a central problem for both the psychological laboratory and the psychiatric clinic, for academic psychologists, psychoanalysts, and psychiatrists alike. There has, however, been little cooperation between them in investigating it. It is essential that a *rapprochement* between the various psychological sciences be accomplished. The issue of unconsciousness offers an excellent occasion to illustrate how this can be achieved. It is only one of many problems in which all branches of the psychological science will find mutual benefit in cooperation. Such a coordinated program is the procedure offering the greatest hope that, in the future, sense can be made in many fields of human personality and behavior which today are realms of ignorance and nonsense.

"The enigma of unconsciousness has been studied and disputed by psychologists for many years. It has been approached from many angles, from the neurological at the one extreme to the philosophical at the other. It has been the subject of careful experimentation on the one hand and of soaring theorizing on the other. The problem has embraced such different phenomena as fainting, hypnosis, inattention, creativity, repression, and instinctual behavior.

"Some who have interested themselves in these questions have seen that all these sorts of unconsciousness cannot be identical, and they have often insisted that they do not even have similar characteristics. Therefore, various terms have been invented, compounds of the word conscious, in order to distinguish and explain these different phenomena. Such words as 'subconscious,' 'preconscious,' 'foreconscious,' 'superconscious,' 'coconscious,' and so forth. The result of this neologizing, however, has not been increased clarity, but greater confusion. Moreover, many dissimilar sorts of behavior are still called 'unconscious' without any effort's being made to define the various senses of this wide term.

"This book attempts to distinguish the various meanings of the word 'unconscious' which have been used, and to describe and differentiate carefully the diverse sorts of human behavior which have been included under this term. Then each of the phenomena is considered at length; the clinically and experimentally determined facts about each one are reviewed; and an evaluation is made of the present state of knowledge on that specific subject. Not until this detailed study of each sort of unconsciousness has been made can the common aspects of them all be thrown into their proper light in a way that is even slightly more than speculative. When such a procedure is followed, however, solid bases for a tentative theory of unconsciousness begin to appear. Only by such an approach can any conclusion be reached as to how conscious behavior is like unconscious and how it is different."

Unconsciousness is discussed and described in the senses commonly in use; there are so many that the word practically loses its usefulness as a medium to convey scientific ideas. The author not only shows this but brings in a wealth of

interesting material, critically evaluated, concerning such subjects as amnesia, volition, insight, attention, suppression and repression. The book is well documented and will repay careful reading by those interested in this central theme of psychology and neurology. It will please no reader who rides a hobby and thinks he already knows the answer.

Conceptual Thinking in Schizophrenia. By Eugenia Hanfmann and Jacob Kasanin. Nervous and Mental Disease Monographs, No. 67. Price $2.50. Pp. 115. New York: Nervous and Mental Disease Publishing Company, 1942.

In the study reported in this monograph, the authors set themselves the task of testing Vigotsky's theory that conceptual thinking suffers impairment in schizophrenic patients. Vigotsky's concept formation test was used. In this test, blocks of various shapes, sizes and colors are presented to the subject, who is expected to sort them into four groups by discovering what combination of characteristics is indicated by nonsense words written on the backs. The subjects tested comprised 62 schizophrenic patients, 24 patients with organic disease of the brain (dementia paralytica and arteriosclerosis) and 95 normal controls. In analyzing the performance of each subject, the authors recognized three major phases: (1) the interpretation of the instructions; (2) the attempts at solution, and (3) the finding and mastering of the correct solution. In each of these phases of performance three levels of performance were distinguished: (1) the extremely primitive, "concrete" performance; (2) a performance in which certain aspects of conceptual thinking were present and others absent, and (3) the performance based on fully developed conceptual thinking. A quantitative method is presented for evaluating the performance of each subject in terms of these levels.

The results obtained by this method of analysis of the subjects' performance are reported in detail. Several of them seem of particular interest. For instance, a close relationship was noted between performance at the highest conceptual level and high educational level. To this reviewer, the authors seem, at this point, to overlook the opportunity for clarifying the basic question as to whether this relationship is not actually one between intelligence level and high performance. Even among the normal subjects only the college-educated group performed on the highest conceptual level, the noncollege normal subjects performing at the intermediate level. Among the college-educated schizophrenic subjects a wide variation of performance was found, one-third showing superior conceptual performance and another third a primitive performance that fell far below the average even of the uneducated normal subjects. The schizophrenic group was sorted out on the basis of various clinical syndromes and the level of performance determined for each group. Unimpaired conceptual thinking was found most frequently in the group of patients characterized by prevalence of neurotic symptoms, while impairment was most evident in the groups showing (1) disturbance of intellectual function expressed in a tendency to incoherence and irrelevance, (2) marked dissociation with extensive fantastic elaboration of ideas and (3) a paranoid-hebephrenic trend with dull affectivity. While these observations seem to indicate that impairment in conceptual thinking is not, as Vigotsky claimed, the central disturbance in schizophrenic thinking, although it may be found in cases in which the personality is grossly affected, the authors formulate their conclusions rather confusingly by stating that their study "confirms" Vigotsky's thesis that conceptual thinking suffers impairment in schizophrenia. They take issue with Vigotsky's dichotomy of conceptual and "primitive" thinking, which they regard as inadequate, but do not comment on the factor of "regression," which he stresses.

Observations on the schizophrenic subjects and the patients with organic disease are compared, but the differences are less convincing.

The final chapter is devoted to a discussion of the authors' findings in the light of other studies on thinking recorded in the literature.

This study is provocative and stimulating and represents an interesting contribution to the literature of schizophrenic thinking. There is a list of references of sixty-one titles and an index.

The Biologic Fundamentals of Radiation Therapy. By Friedrich Ellinger. Price $5. Pp. 360, with illustrations. Amsterdam: Elsevier Publishing Co. (New York: Nordemann Publishing Company, Inc.), 1941.

The book is divided into five parts. The first is devoted to a discussion of the action of roentgen rays and the gamma radiation of radium on the various tissues of the body. In many instances the dose of radiation that produces a reversible or an irreversible reaction in the tissues is given. In the second part are described the corpuscular rays and their effect on the body. In the third part ultraviolet light and its action, both direct and indirect, are discussed. Among the direct effects, to name but a few, sunburn and the bactericidal and antirachitic action of the rays are discussed, while among the indirect effects the action of the light on metabolism, respiration, circulation, the blood and the endocrine glands and its use in the treatment of tuberculosis are discussed. In the fourth part of the book attention is given to such subjects as the action of visible light, infra-red rays, the intensification of the action of light and diseases caused by light. The last, or fifth, part of the monograph is concerned with the theories of the effects of radiation, radiosensitivity, the time factor and the general principles for the application and dosage of radiation in therapy. There is a valuable bibliography of 1,100 articles. The author and subject indexes are excellent.

The author is conservative in the presentation of his subject matter. The book is an excellent one and contains an immense amount of accurate and valuable information for the radiologist and for the student. It is a book that every one who is interested in radiation therapy should own.